ANNALS OF INTERNAL MEDICINE

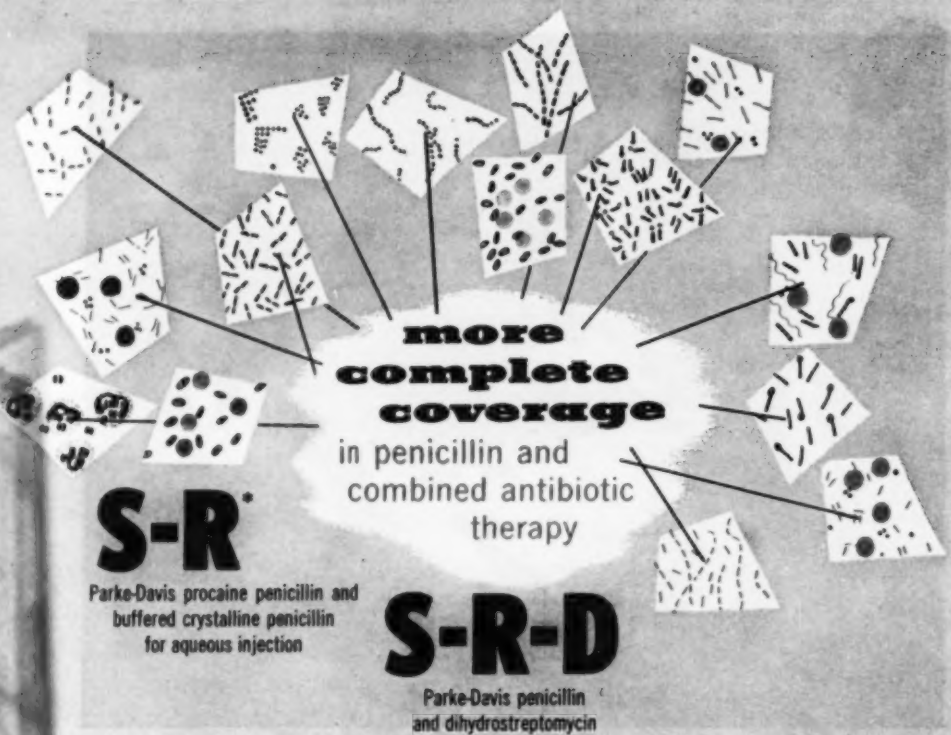
PUBLISHED MONTHLY BY

The American College of Physicians

VOL. 37 (O.S., Vol. XLII) SEPTEMBER, 1952 NUMBER 3

Subscription per annum, net postpaid, $10.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico, Philippine Islands, Central and South American Countries, and Spain; $11.00, other countries.

Entered as Second Class Matter August 21, 1933, at the Post Office at Lancaster, Pa., under the Act of March 3, 1879. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph (d-2), section 34.40, P. L. & R. of 1948, authorized October 7, 1936.



more complete coverage

in penicillin and combined antibiotic therapy

S-R*

Parke-Davis procaine penicillin and buffered crystalline penicillin for aqueous injection

S-R-D

Parke-Davis penicillin and dihydrostreptomycin

Penicillin-sensitive organisms yield to the S-R combination. For effective action against either penicillin-sensitive or dihydrostreptomycin-sensitive organisms, clinicians will find the S-R-D formula especially valuable. Between them, these two effective antibiotic combinations provide broad coverage against such organisms, for they produce the prolonged high serum levels needed for control of infection.

S-R-D has a broader antibacterial spectrum, producing the "cross-fire" action so effective in combating mixed infections.

S-R and S-R-D suspensions are simply prepared, insure ease of injection, and are completely absorbed with minimal pain. They contain no added suspending agent or sensitizing diluent.

Suspensions of S-R and S-R-D are prepared by adding a suitable diluent, which may be Water for Injection, Physiological Sodium Chloride Solution, or 5 per cent Dextrose Injection. S-R is available in packages containing 400,000 units (1 dose), 2,000,000 units (5 dose), or 4,000,000 units (10 dose), of the S-R combination in the ratio of 300,000 units procaine penicillin-G with 100,000 units buffered crystalline sodium penicillin-G. S-R-D provides in each single dose package the S-R combination (400,000 units penicillin) plus either 1 Gm. or 1 Gm. of dihydrostreptomycin; both also available in 5-dose packages.

MEDICAMENTA VERA

Parke, Davis + Company

*TRADE MARK

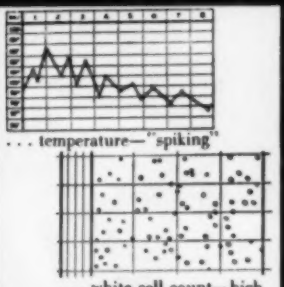
URINARY TRACT

Pyelonephritis

Pyelonephritis occurs most often in the young child . . .

commonest in the "diaper-age" female

The onset is sudden, usually with a chill . . .



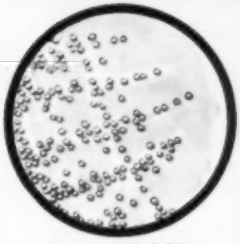
. . . temperature—"spiking"

. . . white cell count—high

Always, pus cells and bacteria appear in the urine

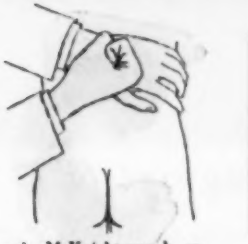
look for *clumps* of white cells in *catheterized* specimens

Culture determines pathogen. Mixed infection not uncommon.



in 8 out of 10 children, colon bacillus invades

Sometimes there is tenderness over the kidney region . . .



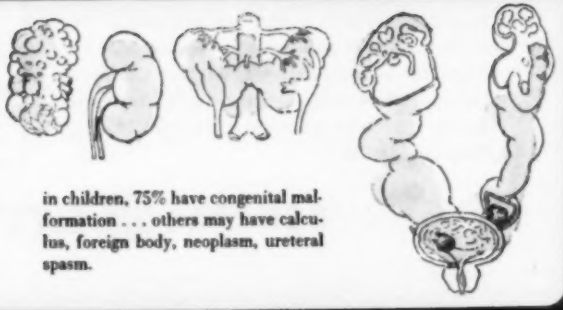
try the McKnight punch, or

palpation in C.V angle

. . . or abdominal pain and rigidity

suggestive of an acute abdomen

Look for a cause of urinary stasis.



in children, 75% have congenital malformation . . . others may have calculus, foreign body, neoplasm, ureteral spasm.

INFECTIONS

CRYSTALLINE

Terramycin

Many urinary tract infections
as well as other infections
rapidly respond to therapy
with this well-tolerated
broad-spectrum antibiotic

Available in a wide variety of convenient dosage forms.

Pfizer *world's largest producer of antibiotics*

ANTIBIOTIC DIVISION, CHAS. PFIZER & CO., INC., BROOKLYN 6, N.Y.

new

convenient

ANDROGEN THERAPY

for women

ORETON-M Buccal Tablets

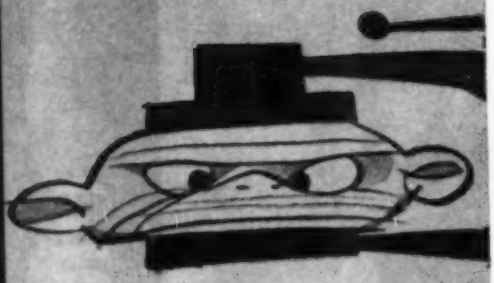
ORETON-M Buccal Tablets containing methyltestosterone dissolved in POLYHYDROL,® a unique solid solvent, provide a more effective and convenient form of male sex hormone. The buccal route permits methyltestosterone to reach the circulation directly. Indicated for definitive relief of menopausal symptoms in special circumstances; for preventing pain of functional dysmenorrhea; and to relieve discomfort of breast engorgement.

Freedom from masculinizing side effects can be expected with recommended dosage of one-half to one and one-half 10 mg. ORETON-M® (Methyltestosterone U.S.P.) Buccal Tablets daily (5-15 mg.).

ORETON-M

buccal tablets

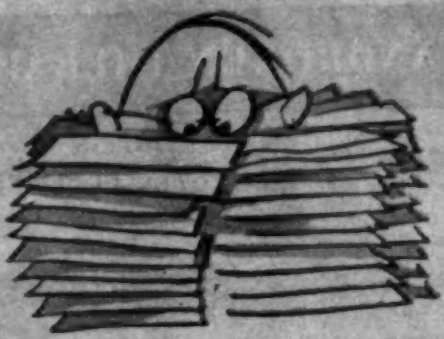
Schering CORPORATION • BLOOMFIELD, NEW JERSEY



pressure

When

diet



work

worry

emotional disturbances

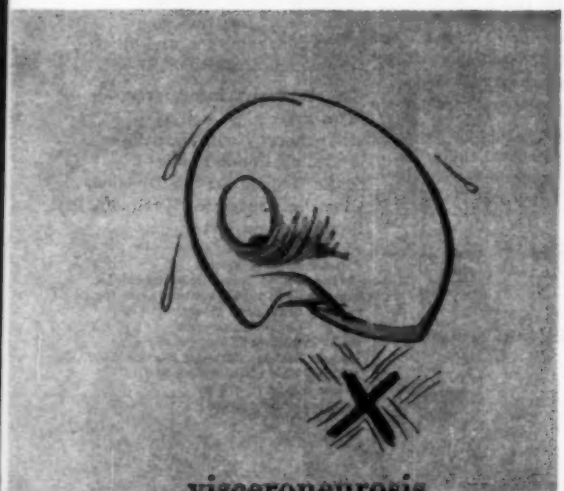
pressure, diet, work, worry,

emotional disturbances, visceroneurosis

cause ***Nervous Indigestion*** . . .

BENTYL

offers effective, comfortable, sustained relief from pain, cramps, general discomfort due to functional gastrointestinal spasm. In clinical studies[1,2,3] BENTYL gave gratifying to complete relief in 308 of 338 cases, yet was ". . . virtually free from undesirable side effects."[3]



EACH CAPSULE OR TEASPOONFUL SYRUP CONTAINS:

BENTYL . . . . . **10 mg.**
For safe, double-spasmolysis

BENTYL . . . . . **10 mg.**
with **PHENOBARBITAL** . . . . . **15 mg.**
When synergistic sedation is desired

DOSAGE—ADULTS: 2 capsules or 2 teaspoonfuls syrup 3 times daily, before or after meals. If necessary, repeat dose at bedtime.

IN INFANT COLIC: ½ to 1 teaspoonful syrup 3 times daily before feeding.[4]

Merrell
1828

New York • CINCINNATI • Toronto

1. Hock, C. W.: J. Med. Assn. Ga. 40:22, 1951 • 2. Hufford, A. R.: J. Mich. St. Med. Soc. 49:1308, 1950 • 3. Chamberlin, D. T.: Gastroenterology 17:224, 1951 • 4. Pakula, S. F.: To be published •

Trade-mark "Bentyl" Hydrochloride

A vagal blocking agent for peptic ulcer with LOW incidence of SIDE EFFECTS

PRANTAL* methylsulfate (diphenmethanil methylsulfate) is an effective anticholinergic agent for treatment of peptic ulcer. Pain, pyrosis, nausea, and other symptoms of this syndrome are rapidly relieved. Troublesome side effects seldom occur.

*T. M. Tablets 100 mg. q. 6 h.

Schering CORPORATION
BLOOMFIELD, N. J.
In Canada: Schering Corporation, Ltd., Montreal, Que.

PRANTAL
methylsulfate

PRANTAL

SCHERING

Not three...but Four 4

Four factors are now recognized in the treatment of peptic ulcer...

1. ***Neutralizing hyperacidity.*** KOLANTYL includes a superior antacid combination (magnesium oxide and aluminum hydroxide, also a specific antipeptic) for two-way, balanced antacid activity.

2. ***Protecting the crater.*** KOLANTYL includes a superior demulcent (methylcellulose, a synthetic mucin) which forms a protective coating over the ulcerated mucosa.

3. ***Blocking spasm.*** KOLANTYL includes a superior antispasmodic (Bentyl) which provides direct smooth-muscle and parasympathetic-depressant qualities . . . without "belladonna backfire."

And only KOLANTYL includes the important 4 th factor

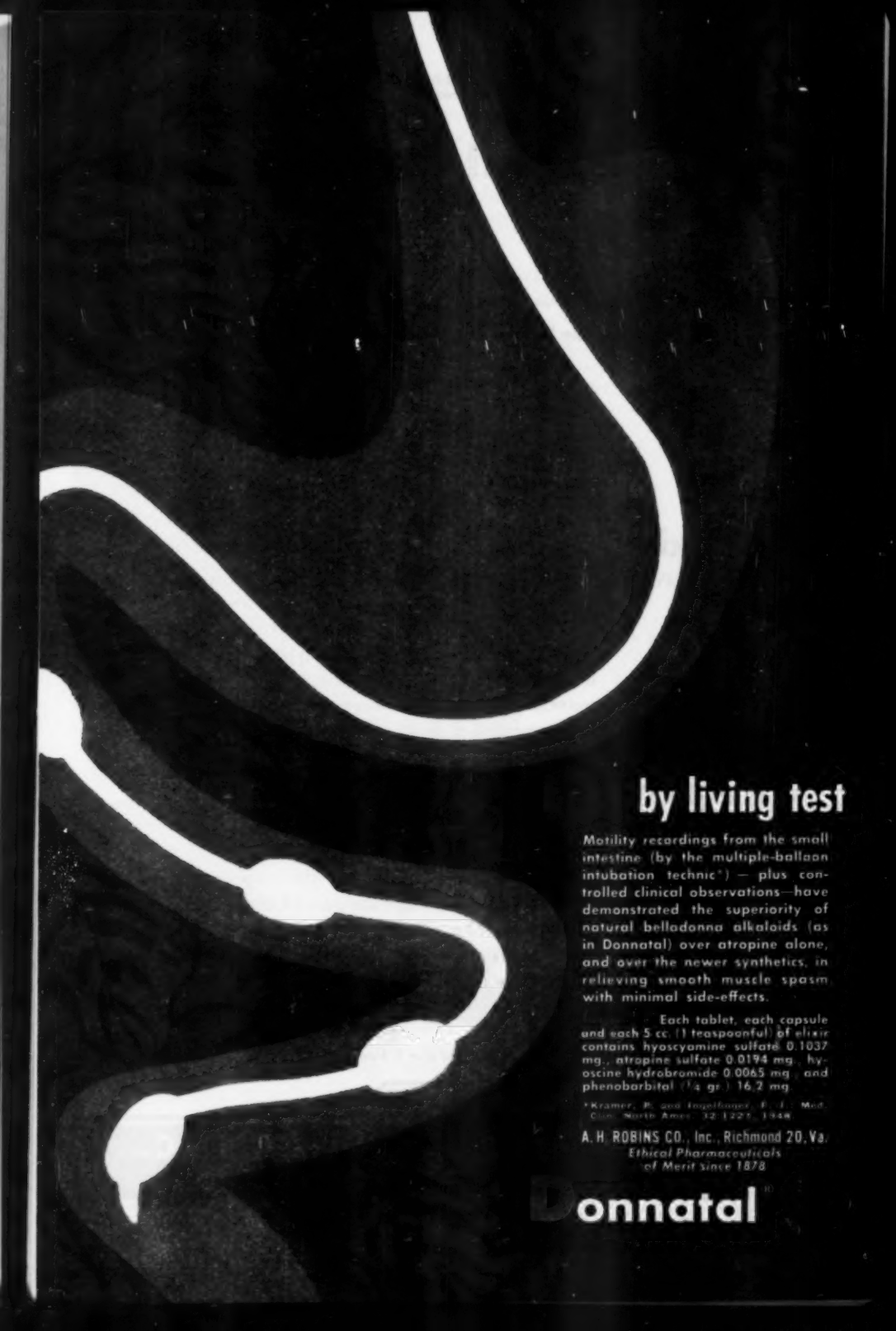
4 ***Inactivation of lysozyme . . .*** with a proven antilysozyme, *sodium lauryl sulfate.* Laboratory research[1,2,3] and clinical results[4] indicate that the enzyme lysozyme is one of the etiologic agents of peptic ulcer. By inhibiting or inactivating lysozyme, KOLANTYL—and *only* KOLANTYL—provides the important 4th factor toward more complete control of peptic ulcer.

Merrell
1828

New York · CINCINNATI · Toronto

DOSAGE: Two tablets every three hours as needed for relief. Mildly minted, Kolantyl tablets may be chewed or swallowed with ease.

1. Meyer, K. et al. Am. J. Med. 5:482, 1948. 2. Wang, K. J. and Grossman, M. I. Am. J. Phys. 155:476, 1948. 3. Grace, W. J. Am. J. Med. Sc. 217:241, 1949. 4. Hufford, A. R. Rev. of Gastroenterology, 18:588, 1951.



by living test

Motility recordings from the small intestine (by the multiple-balloon intubation technic*) — plus controlled clinical observations—have demonstrated the superiority of natural belladonna alkaloids (as in Donnatal) over atropine alone, and over the newer synthetics, in relieving smooth muscle spasm with minimal side-effects.

Each tablet, each capsule and each 5 cc. (1 teaspoonful) of elixir contains hyoscyamine sulfate 0.1037 mg., atropine sulfate 0.0194 mg., hyoscine hydrobromide 0.0065 mg. and phenobarbital (1/4 gr.) 16.2 mg.

*Kramer, P. and Engelhart, R. J.: Med. Clin. North Amer. 32:1227, 1948

A. H. ROBINS CO., Inc., Richmond 20, Va.
Ethical Pharmaceuticals of Merit since 1878

Donnatal®

ANNALS OF
INTERNAL MEDICINE

VOLUME 37 SEPTEMBER, 1952 NUMBER 3

ELECTROLYTES AND CONGESTIVE FAILURE*

By T. S. DANOWSKI, F.A.C.P., *Pittsburgh, Pennsylvania*

IN individuals with an efficient circulation, adequate renal function and an effective endocrine system, a variety of adjustments contrives to maintain body water and electrolyte stores quite constant.[1a-c] It is now generally acknowledged that these mechanisms are no longer normally operative in congestive failure. The increases in body sodium, chloride and water which constitute the edema of congestive failure must be based ultimately on an undue retention of these constituents as taken in the diet. It is appropriate, therefore, to review the evidence which points to etiologic and contributory factors in producing such positive balances of body water and electrolytes. Such a survey yields a large body of information which immediately brings to mind the Hampton Maze. The opportunities for wrong turns, for confusion and for frustration are quite reminiscent of some of our clinical and investigational experiences in complicated biologic problems in general and in congestive failure in particular. Segments of such a maze illustrate the flow of ideas, facts and deductions as they relate to certain aspects of electrolyte and water metabolism in congestive failure.

INQUIRIES CONCERNING THE ADEQUACY OF MYOCARDIAL FUNCTION AS A FACTOR IN EDEMA

More than a century ago, James Hope voiced the then prevalent view that the manifestations of cardiac decompensation were directly related to weakening of the myocardium, with consequent accumulation of blood on the venous side of the two ventricles.[2] The notion that the failure of the heart to eject adequate amounts of blood into the arterial system may account for some of the manifestations of congestive failure logically suggested itself to Cohnheim when he found a drop in arterial pressure and a rise in venous

* Presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 23, 1952.

From the Department of Research Medicine, and the Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine.

pressure in tamponade.[3] Starling's demonstration a few years later that with failure the venous pressure rose with compensatory though limited increases in output in response to myocardial stretching, and that rising venous pressures increased capillary transudation, was taken to provide quantitative support for the rôle of venous stasis in the genesis of edema.[4a, b] Several decades later, Landis expressed the opinion that in heart disease the edema resulted from a combination of hypoproteinemia and venous congestion, and this thesis was incorporated in the clinical views of Harrison.[5a, b] In the interim Mackenzie, feeling that the fundamental alteration in cardiac insufficiency was a deficient cardiac output, stated: "Heart failure may be defined as the condition in which the heart is unable to maintain an efficient circulation when called upon to meet the efforts necessary to the daily life of the individual." [6]

As we shall see in subsequent sections, the fundamental contributions of none of these workers need be discarded, nor can they be disregarded.

The Relative Effectiveness of Systole in Distributing Blood

Today, agreement is uniform concerning the resting cardiac output or index in patients with heart disease and congestive failure: in a particular case it may be less than, equal to, or higher than the mean value obtained in control subjects.[7a-d] Any series of patients in failure, however, will in general be characterized by a diminished cardiac output. If tissue needs are not proportionately decreased, this decrement in cardiac work will understandably result in insufficient supplies to the tissues. In such a group of patients, overlap with the lower limits of normal will be present, and a few patients may actually exceed the upper range in the controls. Instances of the latter, called "high output failures," usually consist of individuals with thyrotoxicosis, anemia, anoxia, beriberi or arteriovenous fistulae occurring alone or in combination.[7c, 8a-c] The Paget's disease group, which may also have a high resting output, is presumably a subdivision of the last of the categories mentioned. This somewhat anomalous situation, in which a heart has succeeded in raising its output considerably above the resting range of normal without alleviating the symptoms and signs of congestive failure, again emphasizes the existence of conditioning factors. In this group of cases the fundamental defect, or at least the currently acceptable common denominator, is a disproportion between the tissue needs and the supplies of oxygen. Since these clinical entities do occur without circulatory failure, the high cardiac output may be viewed as a useful compensatory adjustment. The coexistence of myocardial disease (ignoring, for the moment, such questions as whether hyperthyroidism is itself capable of producing myocardial damage, or merely accelerates the course of underlying disease of some other etiology) results in congestive failure presumably when the myocardium is no longer capable of maintaining the requisite level of work. One might at first thought expect that measures which restore circulatory

efficiency would raise the high output even higher. This does not happen because these same measures, whether they be bed-rest, alleviation of thyrotoxicosis, et cetera, diminish the oxygen needs of the tissues, and a balance between supply and demand is reached at levels below those prevalent in the decompensated phase. This illustration serves to emphasize two established facts: (A) Studies of resting subjects may not reveal discrepancies present during activity between work needed and actual work done, and (B) measurements of the arteriovenous oxygen difference, especially during circumstances in which clinical failure is present, can be more valuable as indices of the relative cardiac efficiency than is the cardiac output itself.

Irrespective of indices employed, it is generally agreed that in clinical congestive failure tissues and organs do not receive an adequate supply of blood and nutrients. Studies of blood and plasma volume suggest that this insufficiency may exist in the face of actual plethora or hypervolemia.[9a-d] This subject is open to further clarification, since the accuracy of measurements of the volume of the vascular compartment has been impugned. Greater agreement, however, is present concerning the venous side of this question: it does appear as though a change was present in the usual venous volume, or in the usual capacity of the venous bed, or in both.[8a, 10a-c] This can be a manifestation of (1) transfers of blood from the arterial to the venous side, (2) over-all expansion of the circulating volume, and (3) increased venous vessel tone, alone or in combination. Irrespective of the mechanisms whereby this is mediated, it is clear that the venous pressure is usually elevated. It inevitably follows that Starling's observations relevant to the hydrostatic pressure and transudation must hold, in both the lesser and the greater circulations, though of course they need not account for all of the manifestations of congestive failure. It is also clear that increases in venous pressure are links in a chain of events which serves to augment stroke volume, that beyond a certain point this compensatory mechanism is no longer operative, and that measures such as tourniquet application, bleeding, sodium restriction, sodium, chloride and water diuresis, and digitalis administration tend to restore circulatory efficiency.[11a-l]

The Sodium Trail

Up to this point sodium, both literally and figuratively, has been carried along in the blood stream as an ill-defined factor in the genesis of congestive failure. I do not know whether Karrel recognized in 1866 that he was practicing sodium restriction in administering limited amounts of milk to cardiac patients.[12] Certainly 50 years ago it was known that administered salt was not excreted promptly in congestive failure, that sodium restriction was beneficial in this condition, and that water intake need not be sharply reduced if sodium was withheld.[13a-c] The accumulation of more precise information was delayed until some 10 years ago, when Schroeder and

Futcher quantified the response of cardiac patients to salt and water loads and found that urinary excretion of administered sodium chloride was retarded and edema augmented.[14a, b] Again water intake appeared to occupy a position of secondary importance with respect to sodium. Since then the work of Schemm has presented us with the obverse of the coin: In some patients, forcing fluid has been found beneficial,[15a, b] perhaps by accelerating sodium loss, while others tolerate such a regimen poorly and may even be harmed.[16a-c]

To pick up the sodium thread which brings us to the current status, we must go back to the careful and ingenious work of Starr. The inability to simulate the hydraulics of congestive failure in mechanical models, save under certain special circumstances, and the observation that venous pressure remained elevated in cardiac failure patients post mortem, led him to suggest that the plasma volume was unduly expanded in congestive failure in relative or in absolute terms, and that its etiology must be sought in extracardiac factors.[17a-d] This expansion could be the result of positive balances of the constituents of edema fluid. There are a number of published examples of precipitation or aggravation of congestive failure by sodium chloride administration.[18a-d] Only scanty and indirect data are available concerning increased assimilation as a factor in shifting the net balances of these ions to the positive side. Even so, the relatively complete absorption of dietary sodium amounting to some 95 per cent or more of that present in the diet [19] makes it unlikely that this factor could add more than a few milliequivalents per day to the load of these electrolytes entering the body fluids. This does not, of course, deny the possible importance of such a mechanism in influencing the effectiveness of agents such as cation exchange resins in augmenting the output of electrolytes in feces.[20] Defective or inadequate excretion, on the other hand, can quickly and markedly augment the body stores of sodium, of chloride and of water, and hence the plasma volume. Since the kidney is the chief pathway for removal of excesses of most electrolytes, it is logical to consider the behavior of these organs in congestive failure. This will require detailed inquiry, and it may therefore be well to dispose first of the rôle of the only other important excretory pathway, i.e., the skin. It has been estimated and approximated by actual measurement that the loss of sodium chloride through intact non-sweating skin surfaces can be as high as 20 mEq. of each ion per day.[16c, 21] There is as yet no direct evidence as to whether congestive failure is associated with decreases in the magnitude of these losses, though observations are recorded concerning the greater insensible water losses [22] and the lowered content of sodium in the sweat of some of these patients.[23] In a sense, the latter observation has only limited application to the problems of altered ion exchanges in congestive failure, since sweating is ordinarily a rare event in subjects with intact or reduced circulatory efficiency.

The Rôle of the Kidney

Virtually all studies of renal circulation during congestive failure have revealed a disproportionate decrease in the flow of blood or plasma through the kidney.[7a, 24a–c] This is accompanied, aggravated or produced by an increase in the vascular resistance of the kidneys.[25a, b] Reduction in the diameter of the efferent arterioles occurring as a part of this renal vasoconstriction raises the volume of blood or plasma which is converted to glomerular filtrate.[26] In net terms, however, the total volume of glomerular filtrate may or may not be reduced below values present without decompensation.[27] This fact has been used as a point of departure for divergent, but surely not mutually exclusive, views concerning the mechanism whereby body salt and water increase in congestive failure. Many of those whose studies have revealed that the load of sodium presented to the proximal tubule via the glomerular filtrate is reduced in amount suggest that this is the primary factor in sodium retention.[24a, 25a, 28a–d] This positive balance of sodium is attributed to tubular reabsorption of sodium at an inflexible and relatively high rate in congestive failure, even though the sodium load is reduced. This in turn decreases the amount of sodium available for urinary excretion and leads to formation or perpetuation of edema. Opposition to this view naturally arose when some congestive failure patients were found to have a normal glomerular filtration rate, or when diuresis or clinical improvement occurred in others without discernible increase in the filtered sodium load.[29a–d] In these circumstances, undue sodium retention eventually had to be ascribed to increased tubular reabsorption.[29d, 30] If tubular reabsorption is accelerated, this change is apparently present in some but not all patients without alteration in the tubular reabsorptive and secretory-excretory capacities.[31a, b]

An interesting observation made in the course of animal studies further indicates the complexity of factors which may be operative in influencing sodium reabsorption. Elevation of renal vein pressure in the dog produces a marked decrease in sodium excretion without alteration in blood flow or in filtration rate.[32] Increased intraabdominal pressure has also been shown to raise renal vein pressure.[33a, b] This has been taken to indicate that intermittent rises in venous pressure, such as those known to occur in clinical or experimental congestion, might account for undue sodium retention.[34a–d] The mechanisms through which the change in sodium loss is mediated remain obscure, but studies stimulated by this finding indicate again that it is not a simple relationship.[35]

Possible Hormonal Influences in Congestive Failure

The factors responsible for increases in Tm_{Na} have not been specifically identified, but the possibility of increases in or increased responsiveness to adrenal cortical steroids which promote sodium reabsorption was logically

raised. The actual data on this point are equivocal, since only certain patients have had evidences of increased adrenal steroid activity or effect.[36a-c]

Hormonal or humoral changes other than those involving the adrenal steroids have been postulated to play a rôle in influencing renal circulation and function. Thus renin has been demonstrated to be present in the blood of a few patients with congestive failure.[37] This factor or VEM may account for the efferent arteriolar constriction.[38] VDM, found in increased concentrations in the hepatic vein of decompensated patients, has a marked antidiuretic activity.[38, 39] Other workers have also demonstrated or suggested the presence of unidentified antidiuretic substances in such patients.[40a, b] Finally, the occasional patient with cyclic premenstrual aggravation of edema brings up the possible rôle of gonadal products in influencing water and sodium exchanges.[41a, b] Whether such pertinent observations point to etiologic factors or merely identify concomitants or sequelae is at this point not apparent. Nonetheless, they do serve to focus interest and research upon conditioning circumstances and hence have been responsible for the less rigid view of the phenomena of congestive failure which now prevails.

Provocative Observations at the Cellular Level

For a number of years it has been known that changes in the electrolyte composition of cells may be present in congestive failure. These have usually consisted of increases in cell sodium and decreases in cell potassium evident on analysis of tissues.[42a-d] Understandable doubt has been raised as to whether these changes were really present, or merely represented an artificial admixture of extracellular edema fluid with cell contents during the analytic procedure. The knowledge now available concerning circumstances in which cell potassium and sodium may be altered certainly renders plausible the possibility that congestive failure may exert such influences.[18, b] The problem is, however, somewhat more complicated in most clinical situations since digitalis or its glycosides usually have been administered to patients with a failing myocardium. These compounds are known to produce alterations in the sodium-potassium composition of myocardial and other cells.[43a-e] One is therefore faced in such situations with separation of etiologic factors. Careful studies have been reported, however, which suggest that individuals with congestive failure have cells that are swollen as a consequence, in part at least, of increased osmotic activity of the cell base.[44a-f] This change may be present in the face of decreases in cell potassium with or without increases in cell sodium. With recompensation, diuresis of cell and extracellular water occurs, with a movement of potassium into cells and a decrease in the osmotic activity of cell base. It may well be that the beneficial effects of sodium restriction on the course of vascular and myocardial disease, and the sometimes aggravating effects of sodium ingestion, are mediated through cell changes.[45a-b] The importance of extending such

studies cannot be overestimated, since they represent attempts at quantification of the functioning units.

Summary

Review of some of the history and most of the established facts of congestive failure indicate that what at first appear to be irreconcilable views ultimately turn out to be the opposite ends of a biologic spectrum. Perhaps the most cogent advance in our understanding of "congestive failure" or "congestive heart failure" is the realization that this is a clinical entity with many contributing and conditioning circumstances. Studies of the cell components of body fluid and electrolytes will expand our knowledge of such factors.

BIBLIOGRAPHY

1. (a) Danowski, T. S.: Newer concepts of the role of sodium in disease, Am. J. Med. **10**: 468–480, 1951.
   (b) Danowski, T. S., and Elkinton, J. R.: Exchanges of potassium related to organs and systems, Pharmacol. Rev. **3**: 42–58, 1951.
   (c) Elkinton, J. R., and Squires, R. D.: The distribution of body fluids in congestive heart failure. I. Theoretic considerations, Circulation **4**: 679–696, 1951.
2. Hope, J.: A treatise on the diseases of the heart, 1846, Lea & Blanchard, Philadelphia.
3. Cohnheim, J.: Lectures on general pathology, 1889, New Sydenham Society, London.
4. (a) Starling, E. H.: On the absorption of fluids from the connective tissue spaces, J. Physiol. **19**: 312–326, 1896.
   (b) Starling, E. H.: The fluids of the body, 1909, Archibald Constable and Co., London.
5. (a) Landis, E. M.: The passage of fluid through the capillary wall, Am. J. M. Sc. **193**: 297–313, 1937.
   (b) Harrison, T. R.: Failure of the circulation, 1939, The Williams & Wilkins Company, Baltimore.
6. Mackenzie, J.: Diseases of the heart, 3d Ed., 1914, H. Frowde, London.
7. (a) Seymour, W. B., Pritchard, W. H., Longley, L. P., and Hayman, J. M., Jr.: Cardiac output, blood and interstitial fluid volumes, total circulating serum protein and kidney function during cardiac failure and after improvement, J. Clin. Investigation **21**: 229–240, 1942.
   (b) Stead, E. A., Jr., Warren, J. V., Merrill, A. J., and Brannon, E. S.: The cardiac output in male subjects as measured by the technic of right atrial catheterization. Normal values with observations on the effect of anxiety and tilting, J. Clin. Investigation **24**: 326–331, 1945.
   (c) Stead, E. A., Jr., Warren, J. V., and Brannon, E. S.: Cardiac output in congestive heart failure. An analysis of the reasons for lack of close correlation between the symptoms of heart failure and the resting cardiac output, Am. Heart J. **35**: 529–541, 1948.
   (d) Hickam, J. B., and Cargill, W. H.: Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema, J. Clin. Investigation **27**: 10–23, 1948.
8. (a) Sharpey-Schafer, E. P.: Cardiac output in severe anaemia, Clin. Sc. **5**: 125–132, 1944.
   (b) Brannon, E. S., Merrill, A. J., Warren, J. V., and Stead, E. A., Jr.: The cardiac output in patients with chronic anemia as measured by the technique of right atrial catheterization, J. Clin. Investigation **24**: 332–336, 1945.
   (c) Merrill, A. J., and Cargill, W. H.: Mechanism of edema formation in thyrotoxic heart disease, Am. J. Med. **3**: 502–503, 1947.

9. (a) Gibson, J. G., 2d, and Evans, W. A., Jr.: Clinical studies of the blood volume. III. Changes in blood volume, venous pressure and blood velocity rate in chronic congestive heart failure, J. Clin. Investigation **16**: 851–858, 1937.
(b) Meneely, G. R., and Kaltreider, N. L.: A study of the volume of the blood in congestive heart failure. Relation to other measurements in fifteen patients, J. Clin. Investigation **22**: 521–530, 1943.
(c) Richards, D. W., Jr.: Dynamics of congestive heart failure, Am. J. Med. **6**: 772–780, 1949.
(d) Prentice, T. C., Berlin, N. I., Hyde, G. M., Parsons, R. J., Lawrence, J. H., and Port, S.: Total red cell volume, plasma volume, and sodium space in congestive heart failure, J. Clin. Investigation **30**: 1471–1482, 1951.
10. (a) Stead, E. A., Jr.: Edema of heart failure, Bull. New York Acad. Med. **24**: 607–614, 1948.
(b) Little, J. M.: A unified concept of cardiac failure, Am. J. Med. **7**: 207–215, 1949.
(c) McMichael, J.: Cardiac venous congestion. Its causes and consequences, Am. J. Med. **6**: 651–661, 1949.
11. (a) Richards, D. W., Jr., Cournand, A., Darling, R. C., and Gillespie, W. H.: Pressure in the right auricle of man, in normal subjects and in patients with congestive heart failure, Tr. A. Am. Physicians **56**: 218–221, 1941.
(b) Richards, D. W., Jr., Cournand, A., Darling, R. C., Gillespie, W. H., and Baldwin, E. de F.: Pressure of blood in the right auricle in animals and in man: under normal conditions and in right heart failure, Am. J. Physiol. **136**: 115–123, 1942.
(c) Reichsman, F., and Grant, H.: Some observations on the pathogenesis of edema in cardiac failure, Am. Heart J. **32**: 438–442, 1946.
(d) Landis, E. M., Brown, E., Fauteux, M., and Wise, C.: Central venous pressure in relation to cardiac "competence," blood volume and exercise, J. Clin. Investigation **25**: 237–255, 1946.
(e) Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S., and Richards, D. W., Jr.: Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardio-circulatory disease, J. Clin. Investigation **25**: 639–664, 1946.
(f) Bloomfield, R. A., Rapoport, B., Milnor, J. P., Long, W. K., Mebane, J. G., and Ellis, L. B.: The effects of the cardiac glycosides upon the dynamics of the circulation in congestive heart failure. I. Ouabain, J. Clin. Investigation **27**: 588–599, 1948.
(g) Harvey, R. M., Ferrer, M. I., Cathcart, R. T., Richards, D. W., Jr., and Cournand, A.: Some effects of digoxin upon the heart and circulation in man. Digoxin in left ventricular failure, Am. J. Med. **7**: 439–453, 1949.
(h) Farber, S. J., Alexander, J. D., Pellegrino, E. D., and Earle, D. P.: The effect of intravenously administered digoxin on water and electrolyte excretion and on renal functions, Circulation **4**: 378–386, 1951.
(i) Davies, C. E.: Effect of treatment on renal circulation in heart failure, Lancet **2**: 1052–1057, 1951.
12. Karrel, P.: De la cure de lait, Arch. gén. de méd. **8**: 513–533, 1866.
13. (a) Achard, C., and Loeper, M.: Sur la rétention des chlorures dans les tissus au cours de certains états morbides, Compt. rend. Soc. de biol. **53**: 346–347, 1901.
(b) Merklen, P.: La rétention du chlorure de sodium dans l'oedème cardiaque, Bull. et mém. Soc. méd. d. hôp. de Paris **20**: 725–731, 1903.
(c) Widal and Lemierre: Pathogénie de certains oedèmes brightiques; action du chlorure de sodium ingére, Bull. et mém. Soc. méd. d. hôp. de Paris **20**: 785–788, 1903.
14. (a) Schroeder, H. A.: Studies on congestive heart failure. I. The importance of restriction of salt as compared to water, Am. Heart J. **22**: 141–153, 1941.
(b) Futcher, P. H., and Schroeder, H. A.: Studies on congestive heart failure. II. Impaired renal excretion of sodium chloride, Am. J. M. Sc. **204**: 52–62, 1942.

15. (a) Schemm, F. R.: Certain clinical aspects of the application of water balance principles to heart and kidney disease, Ann. Int. Med. **30**: 92–99, 1949.
(b) Wolf, A. V.: The dehydrating effect of continuously administered water, Am. J. Physiol. **143**: 567–571, 1945.
16. (a) Bridges, W. C., Wheeler, E. O., and White, P. D.: Low-sodium diet and free fluid intake in the treatment of congestive heart failure, New England J. Med. **234**: 573–578, 1946.
(b) Leevy, C. M., Strazza, J. A., and Jaffin, A. E.: Fluids in congestive heart failure, J. A. M. A. **131**: 1120–1125, 1946.
(c) Gorham, L. W., Lester, D. E., Wolf, A. V., and Shultz, H. H.: The relative importance of dietary sodium chloride and water intake in cardiac edema, Ann. Int. Med. **27**: 575–583, 1947.
17. (a) Starr, I., and Rawson, A. J.: Role of the "static blood pressure" in abnormal increments of venous pressure, especially in heart failure. I. Theoretical studies on an improved circulation schema whose pumps obey Starling's law of the heart, Am. J. M. Sc. **199**: 27–39, 1940.
(b) Starr, I.: Role of the "static blood pressure" in abnormal increments of venous pressure, especially in heart failure. II. Clinical and experimental studies, Am. J. M. Sc. **199**: 40–55, 1940.
(c) Starr, I., Jeffers, W. A., and Meade, R. H., Jr.: The absence of conspicuous increments of venous pressure after severe damage to the right ventricle of the dog, with a discussion of the relation between clinical congestive failure and heart disease, Am. Heart J. **26**: 291–301, 1943.
(d) Starr, I.: Our changing viewpoint about congestive failure, Ann. Int. Med. **30**: 1–37, 1949.
18. (a) Proger, S., Ginsburg, E., and Magendantz, H.: The effects of the ingestion of excessive amounts of sodium chloride and water on patients with heart disease, Am. Heart J. **23**: 555–566, 1942.
(b) Warren, J. V., and Stead, E. A., Jr.: Fluid dynamics in chronic congestive heart failure; interpretation of mechanisms producing edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure, Arch. Int. Med. **73**: 138–147, 1944.
(c) Wheeler, E. O., Bridges, W. C., and White, P. D.: Diet low in salt (sodium) in congestive heart failure, J. A. M. A. **133**: 16–20, 1947.
(d) Newman, W., and Fishel, L.: Observations on the daily changes in venous pressure and weight in a case of chronic congestive heart failure, Circulation **1**: 706–711, 1950.
19. Greenman, L., Peters, J. H., Mateer, F. M., Weigand, F. A., Wilkins, D., Tarail, R., Rhodes, G., and Danowski, T. S.: Biochemical changes accompanying the ingestion of a carboxylic cation exchanger in the hydrogen, ammonium, sodium, potassium, or calcium form, J. Clin. Investigation **30**: 995–1008, 1951.
20. Berger, E. Y., Quinn, G. P., and Homer, M. A.: Effect of desoxycorticosterone on the colon: its relation to the action of cation exchange resins in man, Proc. Soc. Exper. Biol. and Med. **76**: 601–604, 1951.
21. Freyberg, R. H., and Grant, R. L.: Loss of minerals through the skin of normal humans when sweating is avoided, J. Clin. Investigation **16**: 729–731, 1937.
22. Squires, R. D., Crosley, A. P., Jr., and Elkinton, J. R.: The distribution of body fluids in congestive heart failure. III. Exchanges in patients during diuresis, Circulation **4**: 868–880, 1951.
23. Higbes, D. J., Turner, H. H., Moseley, A. J., and Merrill, A. J.: Mechanisms of salt and water retention in heart failure, Am. J. Med. **7**: 249, 1949.
24. (a) Merrill, A. J.: Edema and decreased renal blood flow in patients with chronic congestive heart failure: Evidence of "forward failure" as the primary cause of edema, J. Clin. Investigation **25**: 389–400, 1946.

(b) Bradley, S. E., and Bradley, G. P.: Renal function during chronic anemia in man, Blood **2**: 192–202, 1947.

(c) Aas, K., and Blegen, E.: The renal blood flow and the glomerular filtration rate in congestive heart failure and some other clinical conditions. The effect of exercise and hypoxemia. A preliminary report, Scandinav. J. Clin. and Lab. Investigation **1**: 22–32, 1949.

25. (a) Mokotoff, R., Ross, G., and Leiter, L.: Renal plasma flow and sodium reabsorption and excretion in congestive heart failure, J. Clin. Investigation **27**: 1–9, 1948.

(b) Maxwell, M. H., Breed, E. S., and Schwartz, I. L.: Renal venous pressure in chronic congestive heart failure, J. Clin. Investigation **29**: 342–348, 1950.

26. Fishman, A. P., Maxwell, M. H., Crowder, C. H., and Morales, P.: Kidney function in cor pulmonale. Particular consideration of changes in renal hemodynamics and sodium excretion during variation in level of oxygenation, Circulation **3**: 703–721, 1951.

27. Farnsworth, E. B., and Krakusin, J. S.: Electrolyte partition in patients with edema of various origins. Qualitative and quantitative definitions of cations and anions in cardiac decompensation, J. Lab. and Clin. Med. **33**: 1534–1544, 1948.

28. (a) Wesson, L. G., Jr., Anslow, W. P., Jr., and Smith, H. W.: The excretion of strong electrolytes, Bull. New York Acad. Med. **24**: 586–606, 1948.

(b) Selkurt, E. E., Hall, P. W., and Spencer, M. P.: Influence of graded arterial pressure decrement on renal clearance of creatinine, p-aminohippurate and sodium, Am. J. Physiol. **159**: 369–378, 1949.

(c) Weston, R. E., Grossman, J., Escher, D. J. W., Mokotoff, R., and Leiter, L.: Pathogenesis and treatment of salt and water retention in congestive failure, M. Clin. North America **34**: 615–628 (May) 1950.

(d) Stead, E. A., Jr.: Renal factor in congestive heart failure, Circulation **3**: 294–299, 1951.

29. (a) Briggs, A. P., Fowell, D. M., Hamilton, W. F., Remington, J. W., Wheeler, N. C., and Winslow, J. A.: Renal and circulatory factors in the edema formation of congestive heart failure, J. Clin. Investigation **27**: 810–817, 1948.

(b) Kattus, A. A., Sinclair-Smith, B., Genest, J., and Newman, E. V.: The effect of exercise on the renal mechanism of electrolyte excretion in normal subjects, Bull. Johns Hopkins Hosp. **84**: 344–368, 1949.

(c) Davis, J. O., and Shock, N. W.: The effect of theophylline ethylene diamine on renal function in control subjects and in patients with congestive heart failure, J. Clin. Investigation **28**: 1459–1468, 1949.

(d) Newman, E. V.: Function of the kidney and metabolic changes in cardiac failure, Am. J. Med. **7**: 490–496, 1949.

30. Dock, W.: Physiological problems in the treatment of heart failure, J. Mt. Sinai Hosp. **13**: 310–317, 1947.

31. (a) Hilden, T.: Glomerular filtration rate and maximal tubular excretory capacity in congestive heart failure, Scandinav. J. Clin. and Lab. Investigation **1**: 305–307, 1949.

(b) Grossman, J., Weston, R. E., Halperin, J. P., and Leiter, L.: The nature of the renal circulatory changes in chronic congestive failure as reflected by renal tubular maximal functions, J. Clin. Investigation **24**: 1320–1326, 1950.

32. Blake, W. D., Wégria, R., Keating, R. P., and Ward, H. P.: Effect of increased renal venous pressure on renal function, Am. J. Physiol. **157**: 1–13, 1949.

33. (a) Thorington, J. M., and Schmidt, C. F.: A study of urinary output and blood-pressure changes resulting in experimental ascites, Am. J. M. Sc. **165**: 880–890, 1923.

(b) Bradley, S. E., and Bradley, G. P.: The effect of increased intraabdominal pressure on renal function in man, J. Clin. Investigation **26**: 1010–1022, 1947.

34. (a) Landis, E. M., Brown, E., Fauteux, M., and Wise, C.: Central venous pressure in relation to cardiac "competence," blood volume and exercise, J. Clin. Investigation **25**: 237–255, 1946.

(b) Bradley, S. E., and Blake, W. D.: Pathogenesis of renal dysfunction during congestive heart failure, Am. J. Med. **6**: 470–480, 1949.

(c) Earle, D. P., Jr., Farber, S. J., Alexander, J. D., and Eichna, L. W.: Effect of treatment on renal functions and electrolyte excretion in congestive heart failure, J. Clin. Investigation **28**: 778, 1949.

(d) Maxwell, M. H., Breed, E. S., and Schwartz, I. L.: Renal venous pressure in chronic congestive heart failure, J. Clin. Investigation **29**: 342–348, 1950.

35. Hwang, W., Akman, L., Miller, A., Silber, E., Stamler, J., and Katz, L. N.: Effect of sustained elevation of renal venous pressure on sodium excretion in the unanesthetized dog, Federation Proc. **9**: 65, 1950.

36. (a) Merrill, A. J.: Mechanisms of salt and water retention in heart failure, Am. J. Med. **6**: 357–367, 1949.

(b) Lasche, E. M., Perloff, W. H., and Durant, T. M.: Some aspects of adrenocortical function in cardiac decompensation, Am. J. M. Sc. **222**: 459–467, 1951.

(c) Albert, R. E., and Smith, W. W.: Hemodynamic effects of ACTH, DCA and cortisone compared with congestive heart failure, Am. J. Med. **12**: 111, 1952.

37. Merrill, A. J., Morrison, J. L., and Brannon, E. S.: Concentration of renin in renal venous blood in patients with chronic heart failure, Am. J. Med. **1**: 468–472, 1946.

38. Mokotoff, R., Escher, D. J. W., Edelman, I. S., Grossman, J., Leiter, L., Weston, R. E., Zweifach, B. W., and Shorr, E.: Studies on vasotropic principles in blood (VEM and VDM) and renal hemodynamics in chronic heart failure, Federation Proc. **8**: 112, 1949.

39. Stead, E. A., Jr.: Circulatory factors in congestive heart failure, Factors Regulating Blood Pressure, 3rd Conference, May 5–6, 1949, pp. 178–202, Josiah Macy, Jr. Foundation.

40. (a) Bercu, B. A., Rokaw, S. N., and Massie, E.: Antidiuretic action of the urine of patients in cardiac failure, Circulation **2**: 409–413, 1950.

(b) Miller, G. E.: Water and electrolyte metabolism in congestive heart failure, Circulation **4**: 270–277, 1951.

41. (a) Thorn, G. W., and Emerson, K., Jr.: The rôle of gonadal and adrenal cortical hormones in the production of edema, Ann. Int. Med. **14**: 757–769, 1940.

(b) Sherer, M. G., and Greer, W. E. R.: Cyclic premenstrual congestive heart failure, New England J. Med. **244**: 973–975, 1951.

42. (a) Harrison, T. R., Pilcher, C., and Ewing, G.: Studies in congestive heart failure. IV. The potassium content of skeletal and cardiac muscle, J. Clin. Investigation **8**: 325–335, 1930.

(b) Calhoun, J. A., Cullen, G. E., and Harrison, T. R.: Studies in congestive heart failure. VII. The effect of overwork on the potassium content of skeletal muscle, J. Clin. Investigation **9**: 405–408, 1930.

(c) Cullen, G. E., Wilkins, W., and Harrison, T. R.: Electrolytes in human tissue. II. The electrolyte content of hearts and other tissues from cases with various diseases, J. Biol. Chem. **102**: 415–423, 1933.

(d) Wilkins, W., and Cullen, G. E.: Electrolytes in human tissue. III. A comparison of normal hearts with hearts showing congestive failure, J. Clin. Investigation **12**: 1063–1074, 1933.

43. (a) Cattell, McK., and Goodell, H.: On the mechanism of the action of digitalis glucosides on muscle, Science **86**: 106–107, 1937.

(b) Wood, E. H., and Moe, G. K.: Studies on the effect of the digitalis glucosides on potassium loss from the heart of the heart lung preparation, Am. J. Physiol. **123**: 219–220, 1938.

(c) Wedd, A. M.: The influence of digoxin on the potassium content of heart muscle, J. Pharmacol. and Exper. Therap. **65**: 268–274, 1939.

(d) Hagen, P. S.: The effects of digilanid C in varying dosage upon the potassium and water content of rabbit heart muscle, J. Pharmacol. and Exper. Therap. **67**: 50–55, 1939.

(e) Boyer, P. K., and Poindexter, C. A.: The influence of digitalis on the electrolyte and water balance of heart muscle, Am. Heart J. **20**: 586–591, 1940.

44. (a) Elkinton, J. R., Winkler, A. W., and Danowski, T. S.: Inactive cell base and the measurement of changes in cell water, Yale J. Biol. and Med. **17**: 383–393, 1944.

(b) Elkinton, J. R., Winkler, A. W., and Danowski, T. S.: Transfers of cell sodium and potassium in experimental and clinical conditions, J. Clin. Investigation **27**: 74–81, 1948.

(c) Squires, R. D., Crosley, A. P., Jr., and Elkinton, J. R.: The distribution of body fluids in congestive heart failure. III. Exchanges in patients during diuresis, Circulation **4**: 868–880, 1951.

(d) Elkinton, J. R., Squires, R. D., and Bluemle, L. W., Jr.: The distribution of body fluids in congestive heart failure. IV. Exchanges in patients, refractory to mercurial diuretics, treated with sodium and potassium, Circulation **5**: 58–73, 1952.

(e) Iseri, L. T., Boyle, A. J., and Myers, G. B.: Water and electrolyte balance during recovery from severe congestive failure on a 50 milligram sodium diet, Am. Heart J. **40**: 706–730, 1950.

(f) Uhl, H. M. S., Alexander, L. C., McCaughey, R. S., Boyle, A. J., Iseri, L. T., and Myers, G. B.: Fluid and electrolyte balance during recovery from high output heart failure due to beriberi, Am. J. Med. **12**: 107, 1952.

45. (a) Dole, V. P., Dahl, L. K., Cotzias, G. C., Eder, H. A., and Krebs, M. E.: Dietary treatment of hypertension. Clinical and metabolic studies of patients on the rice-fruit diet, J. Clin. Investigation **29**: 1189–1206, 1950.

(b) Dole, V. P., Dahl, L. K., Cotzias, G. C., Dziewiatkowski, D. D., and Harris, C.: Dietary treatment of hypertension. II. Sodium depletion as related to the therapeutic effect, J. Clin. Investigation **30**: 584–595, 1951.

TREATMENT OF HYPERTENSION WITH ORAL PROTOVERATRINE*

By S. W. Hoobler, M.D., F.A.C.P., R. W. Corley, M.D., T. G. Kabza, M.D., and H. F. Loyke, M.D., *Ann Arbor, Michigan*

Protoveratrine, a purified derivative of *Veratrum album*,[1, 2] is superior to the alkaloids from *Veratrum viride* which have been used previously in the treatment of hypertension in that, in a carefully adjusted dosage schedule, the blood pressure can be reduced for six to eight hours daily without producing nausea, vomiting or tolerance to the medication. Such temporary remissions in blood pressure are of a magnitude and duration sufficient to afford real relief to the heart and arteries of the hypertensive patient. We have reported elsewhere[3, 4] that parenteral administration of protoveratrine is accompanied by a decline in resistance to blood flow in the renal and peripheral vascular beds. The heart is slowed and its output unchanged or slightly reduced, but the simultaneous decline in total peripheral resistance insures adequate regional circulation and greatly relieves cardiac work. Consequently, we find the drug particularly useful for the patient with hypertensive heart failure.

The present report concerns: (1) evaluation of a satisfactory dosage program for the drug; (2) comparison with *Veratrum viride* derivatives, such as "Veriloid," and (3) review of our clinical experience with protoveratrine in the treatment of severe hypertension.

Dosage and Effects of Oral Protoveratrine

In preliminary trials we found that an oral dose of 0.750 to 1.50 mg. usually produced a fall in blood pressure so striking and so free from side effects that patients severely hypertensive for many years suddenly found themselves with normal blood pressure and yet without the symptoms usually so prominent when the blood pressure is abruptly lowered. A dose slightly larger than the effective one generally produced marked hypotension with nausea and vomiting, whereas a slightly smaller amount had no apparent effect.

We then inquired whether *Veratrum viride* derivatives given in a single dose would be equally effective in lowering the blood pressure without emetic

* Presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 22, 1952.

From the Department of Medicine, University of Michigan Medical School, Ann Arbor, Michigan. Supported by grants from the National Heart Institute, U. S. Public Health Service and Eli Lilly & Co. We are indebted to Dr. Otto Krayer, Professor of Pharmacology, Harvard Medical School, and to Dr. Kenneth Kohlstaedt, Eli Lilly & Co., for the supply of Protoveratrine which they kindly placed at our disposal.

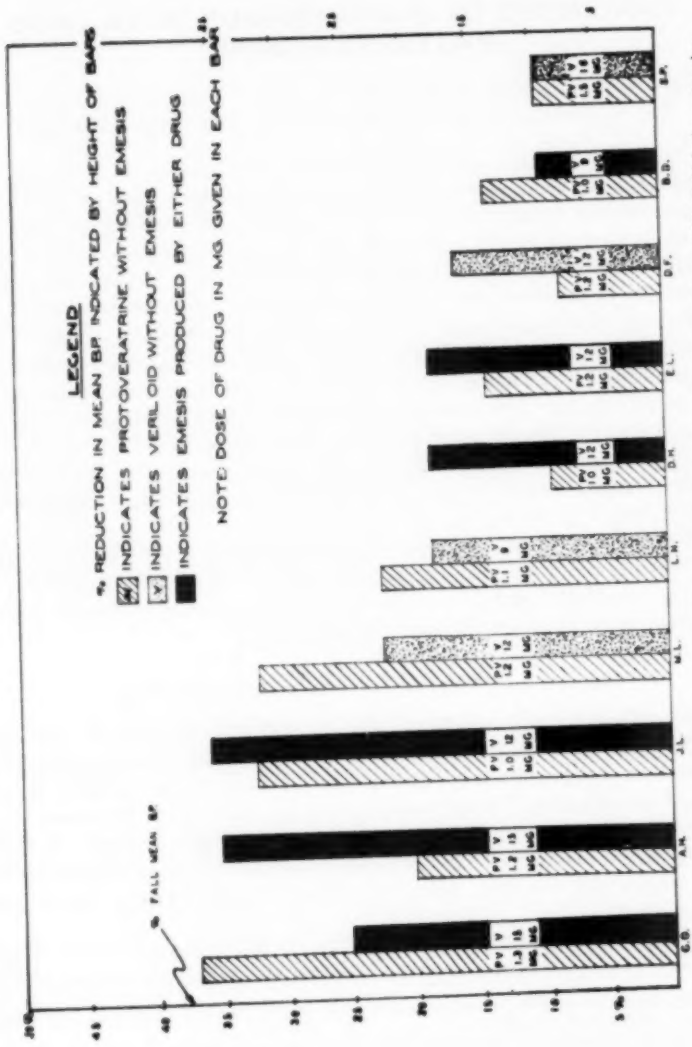


FIG. 1. Comparative hypotensive and emetic effects of single doses of oral protoveratrine and Veriloid in hypertension.

side effects. We chose to compare protoveratrine with Anatensol * and Veriloid. Anatensol given to 15 patients in single doses of 1 to 2 mg. produced less than 10 per cent diastolic blood pressure fall in one-half the cases, and was relatively free of emetic properties. Whether larger dosages would have been more successful is uncertain; we did not extend our study since the five-tablet doses were already well above the usual effective dose as quoted by the manufacturer.

Veriloid given in single effective doses produced nausea and vomiting so frequently as to preclude its use according to the dosage schedule to be recommended for protoveratrine. When smaller doses of the drug were given, no clinical effects ensued (figure 1).

Repeating the single dose of protoveratrine every eight or 12 hours secured a satisfactory and relatively sustained reduction in blood pressure, but usually at the cost of emetic effects after from two to 10 days of continuous therapy. Smaller but more frequent dosage, such as on a four-hourly schedule, produced moderate blood pressure lowering but again at the expense of nausea and vomiting. The effects were such as to suggest that vasodepression preceded by a narrow margin the emetic action of the drug, as postulated in the diagram of figure 2.

We reasoned, therefore, that if an effective dose were reinforced by additional small doses at the time the drug concentration was in the zone of hypotensive action, a more prolonged blood pressure reduction could be secured without exceeding the emetic threshold. This effect was achieved by giving 0.25 mg. of the drug approximately two and four hours after the initial dose. As postulated in figure 2, we found that if the additional dose was given too soon emesis might occur, whereas if reinforcement was given too late no prolongation of action could be expected. The effects of this reinforced dosage program were most satisfactory: emetic side effects were rare, and satisfactory blood pressure reductions were secured which were more sustained than with single doses of the drug (figure 3). We were still unable to give more than one series of doses daily, but we could secure blood pressure reductions during the active hours of the day when the blood pressure was usually highest, or during the night when relief of paroxysmal nocturnal dyspnea was most urgent.

Again we compared the effects of this intermittent treatment program with those achieved by administration of Veriloid in frequent small doses similar to the maintenance program recommended by Wilkins et al.[5] When doses sufficient to produce hypotension were administered, nausea and vomiting occurred frequently. Lesser doses were ineffective (figure 4). Veriloid could not be given in the reinforced dosage recommended for protoveratrine because of the frequent emesis following a single effective dose (figure 1).

* Supplied to us through the courtesy of Dr. H. Sidney Newcomer, Medical Director of E. R. Squibb & Sons, 757 Fifth Ave., New York 22, N. Y.

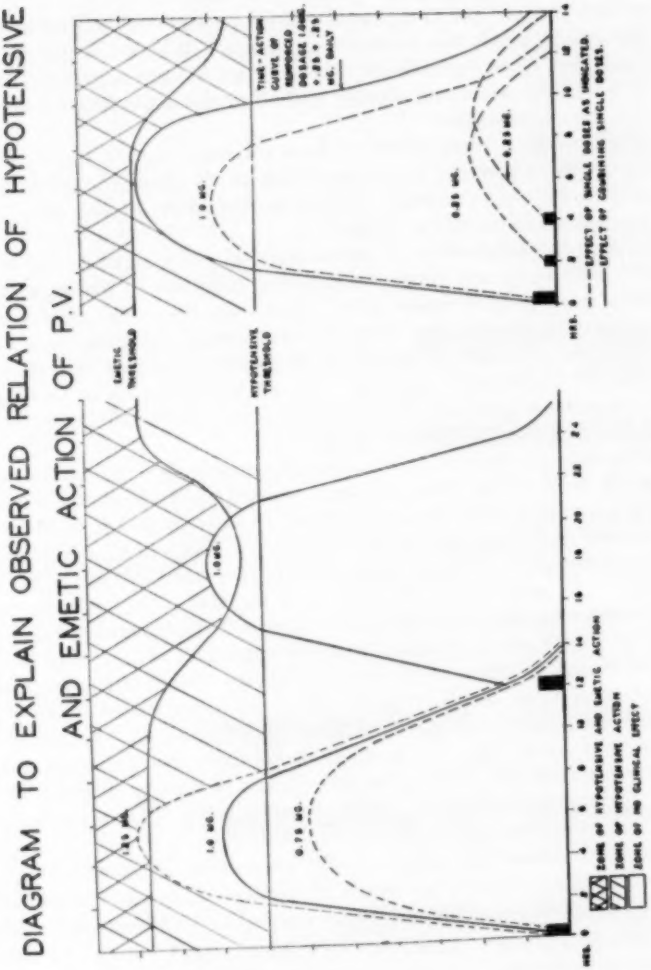


DIAGRAM TO EXPLAIN OBSERVED RELATION OF HYPOTENSIVE AND EMETIC ACTION OF P.V.
EMETIC THRESHOLD
HYPOTENSIVE THRESHOLD
1.5 MG.
1.0 MG.
0.75 MG.
TIME - ACTION CURVE OF REDUCED DOSAGE (.5MG. + .25 + .25 MG. DAILY
1.0 MG.
0.5 MG.
0.25 MG.
HRS. 0
ZONE OF HYPOTENSIVE AND EMETIC ACTION
ZONE OF HYPOTENSIVE ACTION
ZONE OF NO CLINICAL EFFECT
---EFFECT OF SINGLE DOSES AS INDICATED.
——EFFECT OF COMBINING SINGLE DOSES.

FIG. 2.

Technic of Administration

We start with an initial oral dose of 0.75 to 1.0 mg. immediately *after* breakfast in most patients, and increase the initial dose by 0.25 mg. daily until an effective reduction is secured. Usually two additional doses of .25 mg. are given two and four hours after the initial one, care being taken to give no drug within one and one-half hours of the next meal. This results in a gradual reduction in blood pressure and pulse rate lasting for from six to eight hours during the forenoon and afternoon, when the blood pressure of the hypertensive patient is usually at the highest levels. At night, when pressures are usually lowered spontaneously, the effects of the drug are allowed to wear off. If the objective is to treat paroxysmal nocturnal dyspnea, the daily treatment program is started with the evening meal.

Occasionally, alterations in responsiveness to the drug in the direction of increased or decreased sensitivity occur. The dosage may have to be readjusted. For this reason we insist on a day of careful observation every two to four weeks during maintenance therapy. The patient is given the drug in the clinic in the early morning and is followed at half-hourly intervals throughout the day to establish that the given dose remains an effective one.

Side Effects

Treatment in correct dosage is accompanied by very few side effects. There is a burning substernal sensation 20 to 40 minutes after ingestion of the drug, which passes away in about one-half hour. If the dose has been too large, or given at the wrong time, a sense of substernal oppression will result, followed by nausea and vomiting, particularly if food is taken at this time. Vomiting occurs almost invariably if the drug is taken on an empty stomach and food is ingested in the subsequent one and one-half hours. The blood pressure and pulse rate usually fall excessively during such a reaction. Oral atropine, Banthine or Dramamine have little effect in preventing or alleviating these symptoms, although 0.8 to 1.0 mg. of atropine intravenously will abolish the bradycardia and provide considerable symptomatic relief. After a reaction, drowsiness usually ensues. Despite the apparent severity of these reactions at times, we have never seen any serious

Fig. 2. It is supposed that there is a zone in which hypotensive action of the drug can be achieved without emetic effects. However, prior treatment with protoveratrine lowers the threshold of emetic action temporarily so that a second dose within 24 hours may produce nausea. The importance of accurate initial dosage is also demonstrated. An increase of 0.25 mg. from the optimal dose may produce emesis, and a similar decrease may result in no apparent clinical effect.

The rationale of reinforced dosage is presented at the right. Two smaller additional doses given at the correct time, but without clinical effect themselves, will prolong the hypotensive effect of the drug without exceeding the emetic level.

It would appear from our observations that the emetic threshold is also lowered by ingestion of food. It is also possible that Veriloid and other less purified derivatives of *Veratrum viride* have a narrower zone between hypotensive and emetic thresholds and are therefore more likely to produce vomiting when given in single effective doses.

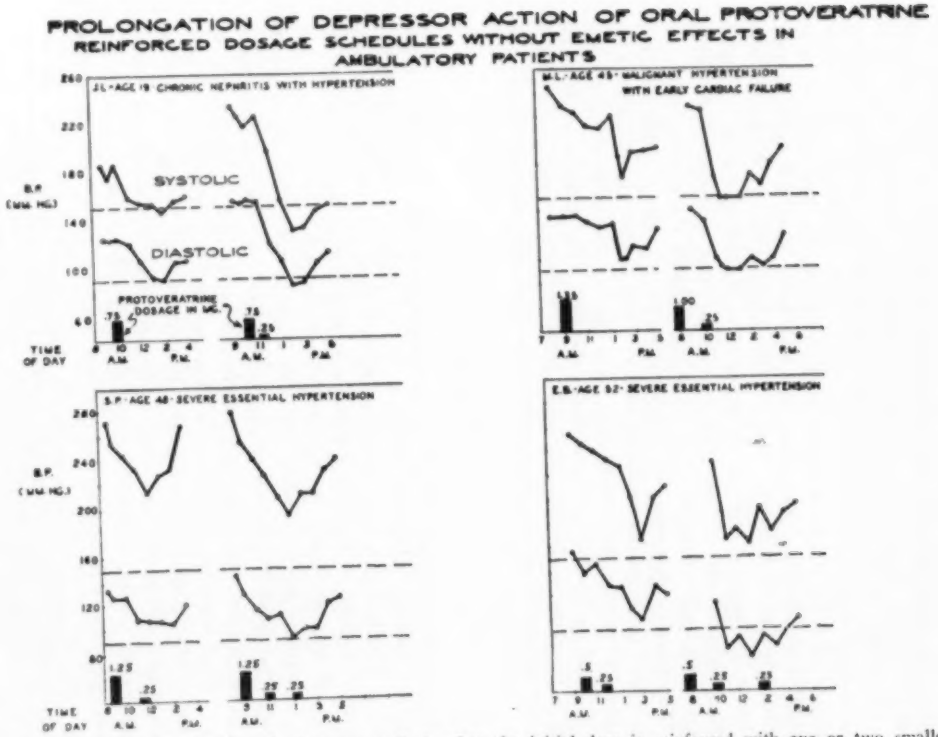


FIG. 3. It will be seen that, in the same patient, when the initial dose is reinforced with one or two smaller doses the reduction in blood pressure tends to be greater and more sustained.

TABLE I

Effect of Continuous Daily Treatment with Protoveratrine on the Blood Pressure in Hypertension of Varied Etiology

Clinic Observations							Dose Range* in Mg.	Duration of Therapy
Name	Diagnosis	No. Visits	Initial BP Range	BP Reduction After				
				Protoveratrine		Placebo		
				Max.	Median	Max.		
G. W.	Chronic Nephritis	10	216–200 / 146–126	46/30	56/24	30/8	0.50	8 mo.
S. P.	Ess. Hypert.	6	290–270 / 144–130	60/36	50/20	+30/22	1.25	5 mo.
D. W.	Ess. Hypert.	9	216–206 / 126–106	76/40	48/24	14/4	1.00–1.25	9 mo.
J. W.	Chronic Nephritis	8	244–195 / 136–118	76/52	78/30	+14/8	1.00–1.25	4 mo.
J. L.	Chronic Nephritis	6	234–194 / 154–130	96/68	76/46	22/2	0.50–0.75	7 mo.
E. B.	Ess. Hypert.	9	244–186 / 142–118	78/50	56/30	6/12	0.50–0.60	6 mo.
S. F.	Ess. Hypert.	7	252–194 / 140–116	56/34	36/24	16/0	1.25	3 mo.
F. M.	Ess. Hypert.	7	236–226 / 146–130	94/50	50/24	—	0.75–1.00	7 mo.
J. E.	Mal. Hypert.	3	250–230 / 140–126	66/44	34/30	—	1.00–1.25	3 mo.
M. L.	Mal. Hypert.	5	260–210 / 146–120	104/62	72/42	—	1.00	4 mo.

Patients took treatment daily at home in the same manner as in the clinic. Slight nausea was never observed in the clinic and was only rarely reported at home. Recumbent blood pressures were recorded in the Hypertension Clinic at half-hour intervals between 9 a.m. and 5 p.m., with the patient ambulatory between observations. The initial blood pressure is taken as the reading after one-half hour in the clinic. The maximal observed reductions in blood pressure represent the greatest observed drop between initial and post-treatment diastolic blood pressure readings, with the corresponding systolic decline. Median reduction is calculated by listing maximal reductions in blood pressure for each clinic visit and selecting that figure which lies midway between greatest and least decline.

* First dose only is indicated. Throughout treatment an additional 0.25 mg. of the drug was given at approximately two and four hours after the first dose.

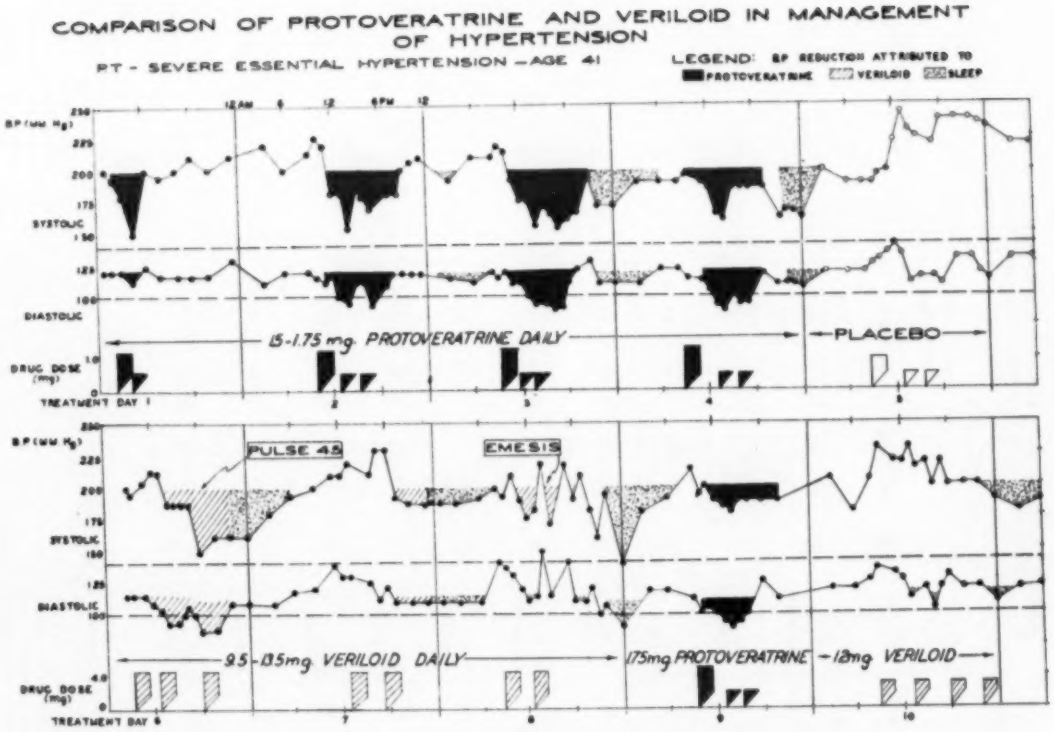

COMPARISON OF PROTOVERATRINE AND VERILOID IN MANAGEMENT OF HYPERTENSION
PT - SEVERE ESSENTIAL HYPERTENSION – AGE 41
LEGEND: BP REDUCTION ATTRIBUTED TO
PROTOVERATRINE
VERILOID
SLEEP
BP (MM Hg)
SYSTOLIC
DIASTOLIC
DRUG DOSE (mg)
TREATMENT DAY
1.5-1.75 mg. PROTOVERATRINE DAILY
PLACEBO
PULSE 45
EMESIS
.95-1.35mg. VERILOID DAILY
.175mg PROTOVERATRINE
1.2mg. VERILOID

FIG. 4.

after-effects, perhaps because we have not elected to treat patients with severe arteriosclerosis. It is remarkable how seldom variations in intestinal absorption lead to any gastrointestinal disturbances once a correct dosage program has been established. The patients may mention slight nausea about once every week or so, which we presume is the result of slightly increased rate or amount of absorption of the drug.

Effects on Blood Pressure

Table 1 and figure 5 summarize our data concerning the effects of this program on the blood pressure. This information is derived from causal half-hourly observations of the blood pressure in patients who remain in the clinic through the day but remain in quiet, sedentary activity. The readings are taken in the recumbent position; a slight orthostatic effect (approximately 30/15 mm. decline) is noted in the standing blood pressure. In some cases, placebo medications have demonstrated that a spontaneous blood pressure decline under these circumstances is not large. It will be seen, therefore, that an appreciable daily blood pressure reduction can be secured over a period of months by the program outlined, with inconsequential side effects from drug action.

Effect on the Heart

Reductions in blood pressure following protoveratrine may provide significant relief for the failing left ventricle. We have shown that cardiac work is greatly decreased by the drug, and clinical observations confirm these experimental findings. The sense of precordial tension and palpitation disappear, gallop rhythm ceases, the previously orthopneic patient can lie flat in bed, and paroxysmal nocturnal dyspnea is often prevented. The heart may become smaller as the result of prolonged therapy. The electrocardiogram shows sinus bradycardia with variable effects on the T waves.

Fig. 4. The blood pressure during the first five days on protoveratrine or placebo treatment is reviewed in the upper half of the figure, while the effects of Veriloid are compared in the lower half. Patient was ambulatory in a hospital ward throughout.

On the first day insufficient reinforcing doses were given. On the second to fourth days satisfactory reductions without side effects were secured through the day and possibly at night (stippled area), although we doubt that drug effect lasts this long. Placebo administered on the fifth day showed that the previous reductions were beyond the spontaneous effects of hospitalization.

On the sixth day, one and one-half tablets (4.5 mg.) Veriloid were given three times a day, with cumulative hypotensive effects and marked bradycardia by evening. The first dose the next morning was omitted by error, and no hypotension resulted. After the second dose on the eighth hospital day, emesis occurred and treatment was stopped. Protoveratrine given on the ninth day reduced the blood pressure without emetic effects. On the tenth day the next smaller dose of Veriloid (one tablet, or 3.0 mg.) was given four times without effect on the blood pressure.

It is concluded from the experience with this and several other cases that frequent small doses of Veriloid are either totally ineffective or frequently produce nausea and vomiting at the level necessary for hypotensive action. Protoveratrine, in reinforced daily doses, produces comparable blood pressure reduction, both in terms of magnitude and in duration of action, without so frequently producing undesirable side effects.

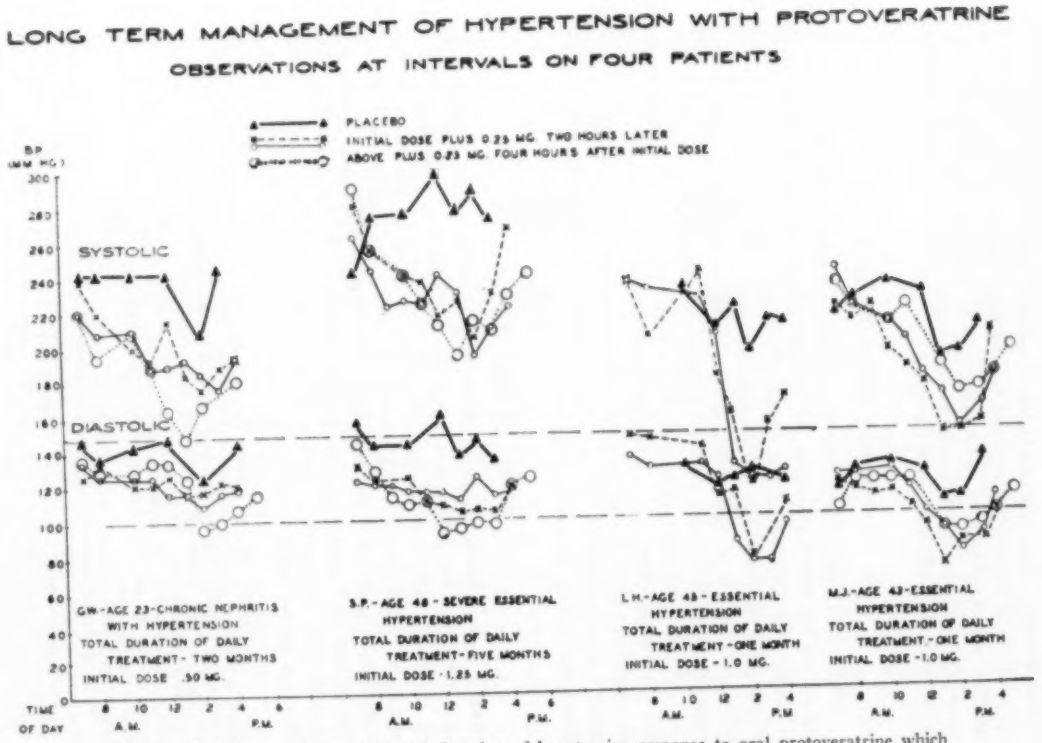


FIG. 5. Graphic record of extent and duration of hypotensive response to oral protoveratrine which occurred in four patients on different clinic visits.

With overdosage, various degrees of heart block may occur, but they are promptly relieved by atropine intravenously. While the cardiac effects of protoveratrine and digitalis are in some respects similar, we have not noticed increased toxic effects from the administration of both drugs to the hypertensive cardiac, although it would probably be better not to digitalize too rapidly a patient on protoveratrine therapy.

The following case histories illustrate our experiences in hypertensive heart disease with protoveratrine:

Case Reports

Case 1. N. P., a 36 year old white male with malignant hypertension, had complained of progressive orthopnea, dyspnea and palpitation for two months before admission. There was a marked tachycardia with gallop rhythm and a definite enlargement of the left ventricle by x-ray. The lungs were clear. Blood pressure was 220/156 mm. of Hg. He was discharged with low sodium diet and digitalis. He returned one month later with recurrence of nocturnal dyspnea and other findings as before. Splanchnicectomy was performed, with no significant effect on the blood pressure.

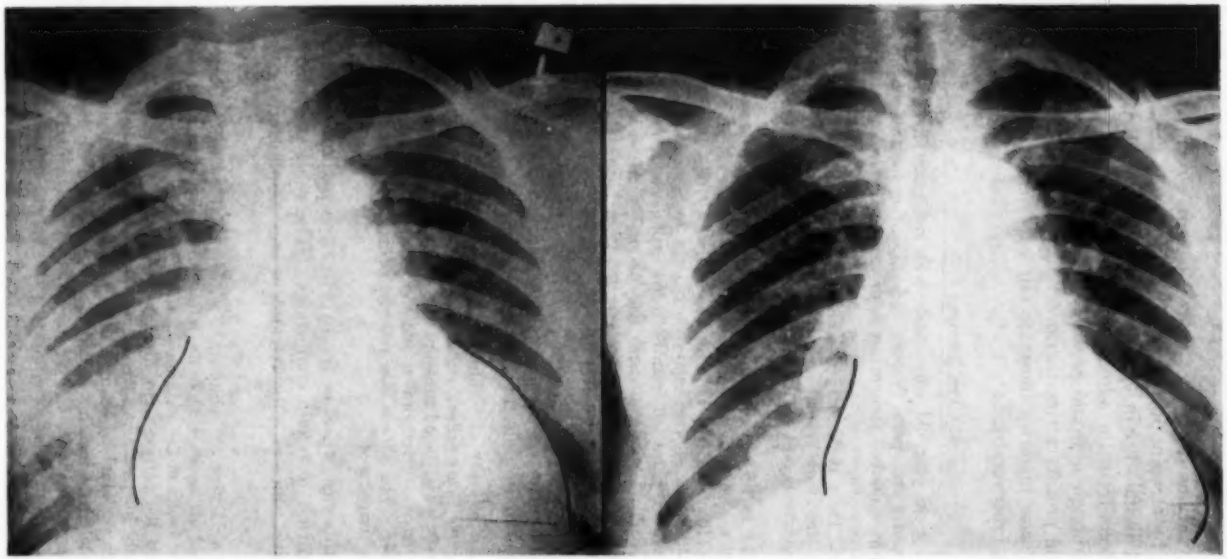
Protoveratrine, 1.0 to 1.5 mg. once and twice daily, was then prescribed for the subsequent two months. Daily blood pressures at home at the height of drug action were: 124/96, 164/110, 150/104, 148/98, 148/104, 146/108, 168/110, 186/144, 184/116, 170/116, 140/98 on alternate days during the first two weeks of therapy. At time of maximal effect, pulse fell from 84 to 64, gallop rhythm disappeared, the palpitation (readily visible to the examiner) was noticeably relieved, and nocturnal dyspnea was no longer present. Venous pressure fell from 125 mm. H_2O to 98 mm. at height of action. Patient noticed marked symptomatic relief during periods of hypotension.

Comment: Severe cardiac hypertensive. Marked reduction of blood pressure with symptomatic relief from protoveratrine.

Case 2. G. B., a 59 year old white female, was admitted to the University Hospital in hypertensive heart failure. She was acutely orthopneic and had moist râles at the lung bases. The blood pressure was 280/150 mm. of Hg. One milligram of protoveratrine was given orally, and the blood pressure fell in two hours to 190/100 mm. of Hg. The patient was relieved of her dyspnea and could lie flat in bed, and the râles disappeared.

Comment: In this case, relief of the hypertension by protoveratrine permitted the left ventricle to regain competence. The relief provided by the drug was impressive, since no other treatment was administered concomitantly.

Case 3. G. C., a 51 year old white male, was hospitalized with a three month history of dyspnea and orthopnea, despite digitalis, diuretics and one week's hospitalization. Within a few hours of the addition of protoveratrine to the treatment régime, dyspnea subsided and the patient slept through the night. Treated daily for one month, he was greatly improved and has returned to work. He has no symptoms except slight dyspnea on climbing stairs. Body weight was unchanged and heart size significantly reduced during this period, despite cessation of diuretic therapy. The details are presented in figure 6. We are indebted to Dr. Mark Marshall and Dr. Joseph McHale, of Ann Arbor, for referring this patient to us.



1/14/52 2/15/52

FIG. 6. Hypertensive heart disease, before and after protoveratrine daily for one month.

TD 20.2 (+70%)

BP 224-170/138-110. Wt. 118 lbs. Heart unchanged October 17 to January 14, by digitoxin, diuretics, diet, 1 week hospitalization. Orthopnea, pulmonary edema.

TD 17.6 (+48%)

BP reduced daily to 130-140/90-100. Wt. 119 lbs. Reduced heart size January 25, February 1 and 15. Only treatment: Protoveratrine, digitoxin, diet. Ambulatory, asymptomatic.

Comment: Remarkable improvement in hypertensive left ventricular failure appeared the result of protoveratrine therapy alone, since the usual therapy had been unsuccessful. Failure to lose weight indicates that improvement was not the result of diuresis. It is believed that the daily reduction in cardiac work by the drug was responsible for the reduction in heart size and partial recovery of competence.

Effect on the Cerebrovascular Manifestations of Hypertension

We have treated a number of patients with hypertensive headaches and dizziness. When good blood pressure reductions have been secured, these symptoms have been clearly relieved. Only a few cases with the more advanced manifestations of encephalopathy have been treated; some, but not all, have benefited, but the successes have been occasionally dramatic, and we believe they could definitely be ascribed to the drug. The following two cases are illustrative:

Case 1. C. O., a 45 year old obese white female, was admitted with a history of having had seven months previously, a right cerebrovascular accident with hemiparesis lasting 10 days. She had had several recurrences of transient paresis in the right leg since this date, during which times she would fall to the ground. In addition, she had complained of blurring of vision and almost daily headaches. Examination revealed obesity, grade III hypertensive retinopathy, and hyperactive reflexes on the right. Blood pressure was 278/154 mm. of Hg. Non-protein nitrogen was 36. She was placed on weight reduction and protoveratrine, 1.25 mg. total daily dose. The following minimal blood pressures after the drug were recorded on nine consecutive visits to the clinic over a six month period: 135/85, 152/80, 150/100, 124/76, 118/90, 142/86, 186/118, 160/96 and 136/80. Headaches cleared, vision improved, and no further encephalopathy occurred. The patient had occasional nausea and vomiting with abdominal pain at home, but gall-stones were found, and the symptoms persisted when protoveratrine was discontinued. She was then given hydrazinophthalazine, up to 150 mg. four times daily for a period of two months, with blood pressure reduction to 200/112, 210/132, 186/114, 184/108 in the clinic on this treatment. The occurrence of headaches and urticaria necessitated discontinuance of the drug. She underwent splanchnicectomy one month later, with a good early postoperative result.

Comment: Improvement in headaches and blurring of vision followed the substantial blood pressure reductions produced over a six month period with protoveratrine. Whereas she had had a number of transient encephalopathic episodes in the seven months before therapy, none occurred in the subsequent six months. In this patient, protoveratrine management was superior to hydrazinophthalazine, in magnitude and duration of blood pressure reduction, and in the relative absence of side effects.

Case 2. J. L., a 15 year old boy with chronic nephritis, was admitted to University Hospital with a history of severe headaches of one year's duration and a recent convulsive seizure. Blood pressure was 170/125 mm. of Hg. There was grade IV retinopathy. Serum creatinine was 5.7 mg. per cent. Another convulsion occurred in the hospital. Following it, .075 mg. protoveratrine intravenously reduced the

blood pressure to 130/100 mm. of Hg, with cessation of the headache and marked decrease in mental confusion. Oral treatment was instituted, using .75 to 1.0 mg. daily, but the headaches returned and the azotemia progressed. However, the headaches were never so severe on protoveratrine therapy as before, and no further convulsions occurred while on this treatment. Patient died in uremia four months later.

Comment: While definite reduction in blood pressure and headaches and relief of convulsive encephalopathy occurred, the treatment was no more than palliative.

Effects on Hypertensive Retinopathy

We have treated a number of patients with moderate azotemia and failing vision from hypertensive retinopathy. Careful measurements of renal function have shown no acceleration of their renal disease, and the improvement of visual acuity and other symptoms in these patients has made us feel this treatment was worthwhile, although only palliative. We believe that if the patient's renal function is adequate, sympathectomy should be attempted, since it is the most likely to arrest the malignant process. If this fails, or if the non-protein nitrogen cannot be brought to normal, the patient is a candidate for protoveratrine treatment, particularly if cardiac, cerebral or retinal failure is impending. If, however, the non-protein nitrogen is above 100, nausea and vomiting as well as the advanced renal failure may be aggravated by protoveratrine. We therefore do not use it in treating hypertension with terminal renal failure.

The following reports are representative of our experience in these cases:

Case 1. J. W., a 38 year old white male, had complained of daily headaches for six weeks, with failing vision for five days. He gave a history of the finding of albuminuria without hypertension following an attack of tonsillitis 17 years before. The fundi revealed early papilledema, with numerous hard exudates forming an incomplete macular star on the left. Visual acuity: right eye, Jaeger type 11; left eye, Jaeger type 13. Blood pressure was 248/150 mm. of Hg. Laboratory findings included 3 plus albuminuria; hemoglobin, 10 gm.; non-protein nitrogen, 69 to 103 mg. per cent; creatinine clearance, 26 to 29 L. per 24 hours. The diagnosis was chronic nephritis. Treatment with protoveratrine, 1.25 mg. total daily dose, was started, with daily reduction in blood pressure varying from 130/92 to 190/118 mm. of Hg. Two months later the patient was back at work, free of headaches, and visual acuity was improved to Jaeger type 14 in both eyes. There had been some further progression of his renal disease, with a 24 hour creatinine clearance of 21.6 L. and a non-protein nitrogen of 100 four months later.

Comment: This chronic nephritic was relieved of headaches, and visual acuity was strikingly improved on protoveratrine. There was some further deterioration of renal function, not incompatible with the spontaneous course of the disease in a near terminal uremic.

Case 2. R. L., a 19 year old white male, was admitted to University Hospital with a history of chronic nephritis and the recent onset of blurring of vision and easy fatigability. He had been on a low sodium diet without improvement. The blood

pressure fluctuated between 240/160 and 170/120 mm. of Hg. The ophthalmologic consultant reported, "Nasal margins indistinct, but no elevation of the disc. Numerous cotton wool exudates. A few superficial flame-shaped and linear hemorrhages. Generalized arteriospasm. . . . There is macular edema with early formation of a macular star temporally and two punctate hemorrhages." Non-protein nitrogen was 48 mg. per cent, and urea clearance was 38 and 14 per cent of normal on two successive urine collections. Patient was started on protoveratrine, 0.5 mg. initial dose and .25 mg. two and four hours later, with daily reductions in blood pressure ranging from 140/90 to 176/116 mm. of Hg during the subsequent nine months of observation. Visual acuity returned to normal; the patient was less fatigued and returned to work. Five months after beginning treatment, the ophthalmologist reported, "Disc normal . . . nasal margins indistinct . . . just inferiorly and temporally to the disc, and superiorly there are cotton wool exudates. Macular edema, previously described, has completely subsided, and there remain some pigmented changes with a few yellowish punctate deposits. No hemorrhages." The non-protein nitrogen five months after beginning treatment was 69 mg. per cent.

Comment: Again improvement in retinopathy occurred, with recovery of visual acuity, probably the result, in part, of repeated reductions in arterial pressure. The increase in non-protein nitrogen has been gradual and is not incompatible with the spontaneous course of the disease.

Case 3. G. W., a 30 year old white male with chronic nephritis and severe hypertension, was referred to the clinic after being rejected for sympathectomy when a non-protein nitrogen of 57 mg. per cent was obtained. He had come to University Hospital because of severe headaches and fatigue, which had necessitated his stopping his work. The blood pressure was 221/123 mm. of Hg, and the patient gave the history and urinary findings of chronic nephritis. His blood pressure responded strikingly to protoveratrine, 0.75 mg. twice daily, with maximal daily reductions on four successive clinic visits to 140/84, 170/112, 152/96, 168/104. Headaches disappeared and he returned to work. We had attempted, however, to give the drug twice daily, and the patient had experienced nausea and vomiting on a number of occasions.

Treatment was discontinued, but the patient returned in a few weeks complaining of recurrence of headaches and fatigue. The reinforced dosage program of 0.5 mg.–.25 mg.–.25 mg. once daily was started, with daily reductions to 176/116 to 150/100 mm./Hg, complete absence of headaches, and lessened fatigue. The patient returned to work and has had no nausea or vomiting. The non-protein nitrogen was 57 mg. per cent eight months after starting treatment.

Comment: Patient markedly improved symptomatically and able to return to work with help of treatment. While treatment is largely symptomatic, its importance is accentuated by the fact that symptoms recurred when it was discontinued. It is gratifying to note that the non-protein nitrogen has not risen during the period of treatment.

Asymptomatic Essential Hypertension

We have not treated many patients with moderate forms of this disease, because of the shortage of drug supply, the relatively benign nature of this stage of the disease, and the difficulty of drawing conclusions as to the clinical benefits of therapy. However, a few cases have been treated with

moderate success. Absolute reductions in blood pressure have been less dramatic, but it is frequently possible to restore the blood pressure to normal levels for part of each day.

Selection of Patients for Treatment

Since this form of treatment is clearly palliative rather than curative, we tend to restrict its use to patients with serious hypertensive symptoms, such as hypertensive heart failure, retinopathy with visual impairment, impending cerebral hemorrhage or encephalopathy, and severe hypertensive headaches. All forms of hypertension appear to respond to treatment. We have been able to reduce the blood pressure in such diverse diseases as poliomyelitis, chronic nephritis, toxemia of pregnancy and malignant nephropathy. We do not treat patients with advanced azotemia unless the previously mentioned symptoms dominate the clinical picture. We also hesitate to treat patients with severe generalized arteriosclerosis or with a history of recent cerebral thromboses, since such individuals often feel worse when their blood pressure is lowered by treatment. We have had no experience with the treatment of angina pectoris in hypertensive patients.

About 10 to 20 per cent of patients will be treatment failures. We abandon treatment in some because they are unusually susceptible to the emetic effects of the drug, and no hypotensive dose of protoveratrine can be found which does not produce nausea or vomiting. It is found on close questioning, however, that many patients who apparently fall into this category have disregarded our advice to take the drug only on a full stomach or more than one and one-half hours before the next meal. Others have developed a reduced tolerance and can be regulated on a lesser initial dose. Some patients, despite all attempts at careful adjustment of therapy, continue to have nausea too frequently to justify further treatment. We also find a few patients who appear refractory to the usual clinical doses of the drug. In our experience, if a patient does not respond when the initial dose has been increased to 1.5 mg., it is unlikely that his blood pressure will be satisfactorily regulated by giving larger amounts of the drug.

Intermittent reduction of blood pressure by drugs is certainly less satisfactory than a good result from surgical or dietary management. We use this treatment only where other methods of management have failed or are inapplicable. Treatment with hexamethonium produces more continuous blood pressure lowering and is probably preferable for in-patient therapy, especially when nausea and vomiting interfere with absorption of protoveratrine. However, when it is desired to manage the patient on an ambulatory basis, treatment may be changed to protoveratrine, which produces a less prolonged but more tolerable hypotension. Our experience with Apresoline indicates that it is less satisfactory than protoveratrine for oral therapy, and that, even when reductions in blood pressure are secured, they are often less in magnitude and duration than with protoveratrine.

Summary

Orally administered protoveratrine, a purified derivative of *Veratrum album*, is useful in the long-term treatment of patients with severe hypertension of diverse etiology. The following dosage program *must be adhered to* if satisfactory results are to be secured:

1. Give initial large dose (.50 mg. to 1.5 mg.) after breakfast, e.g. at 8:00 a.m.
2. Follow with small dose (.25 mg.) reinforcing dose at 10:00 a.m.
3. Second small dose (.25 mg.) reinforcing dose after lunch, 1:00 p.m.
4. Above program only once daily.
5. Caution patient to take tablets after meals or not less than one and one-half hours before the next meal.

When the above program is followed, significant daily reductions in blood pressure lasting six to eight hours may be secured in most patients without the occurrence of nausea and vomiting. The drug is superior to the *Veratrum viride* derivative Veriloid, which produces, in our experience, too frequent emetic side effects to be satisfactory for the long-term management of hypertensive patients. Evidence is presented that the hypotensive action of the drug is particularly useful in the treatment of left ventricular failure. Restoration of vision in malignant hypertension and relief of hypertensive headaches and encephalopathy are also notable beneficial effects. It is emphasized that management of the hypertensive patient with protoveratrine is palliative rather than curative, and that its field of particular usefulness is in alleviating symptoms and lowering blood pressure in patients in whom surgical or dietary treatment is unsuccessful or inapplicable.

BIBLIOGRAPHY

1. Krayer, O., Moe, G. K., and Mendez, R.: Protoveratrine: its comparative toxicity and its circulatory action, J. Pharmacol. and Exper. Therap. **82**: 167, 1944.
2. Meilman, E., and Krayer, O.: The action of protoveratrine and Veratridine in hypertension, Circulation **1**: 204, 1950.
3. Hoobler, S. W., and Corley, R. W.: The hypotensive action of protoveratrine, U. of Mich. M. Bull. **16**: 362, 1950.
4. Hoobler, S. W., Corley, R. W., and Kabza, T. G.: Effects of protoveratrine on the circulation in hypertension (abstract), Am. J. Med. **12**: 110, 1952.
5. Wilkins, R. W., Stanton, J. R., and Freis, E. D.: Essential hypertension. Therapeutic trial of Veriloid, a new extract of *Veratrum viride*, Proc. Soc. Exper. Biol. and Med. **72**: 725, 1949.

EVALUATION OF DEVELOPMENTS IN THE SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS *

By J. Burns Amberson, M.D., F.A.C.P., *New York, N. Y.*

The picture of tuberculosis today contains its lights and shadows. The death rate is only about one-tenth of that in 1900, and the chance of acquiring the infection in childhood is less and less. Yet the disease is still the chief cause of death among those from 15 to 34 years of age, and it accounts for 3 per cent of all deaths in the United States each year. Those who fall sick with it and receive good treatment can now expect to live longer with recovered health than ever before. Toward this happy circumstance thoracic surgery is making important contributions.

Surgery for pulmonary tuberculosis has emerged only in the last two or three decades from the period when it was undertaken only in desperation after all other measures for relief had failed. Improvements in technical procedures, in anesthesia and in the training of young surgeons have sped the change, aided by important extensions of our knowledge of the pathogenesis and prognosis of the disease. All this and the availability of specific drugs have necessitated a reorientation of the principles of treatment, a transition which is still in progress.

Among adolescent and adult tuberculous patients, the usual form of the disease is pulmonary. The first manifest lesion, with very few exceptions, is a so-called "minimal" infiltrate in one lung. Then, if the disease is not arrested, progression occurs by ulceration and sloughing of this lesion and dissemination of the infection by way of the bronchi. By a continuation and repetition of these mechanisms advanced cavitary disease is established, leading often to disability and death. It is only a slight oversimplification to say that control and healing of the "minimal" lesion prevent disability and death. But if treatment does not achieve this end, or if the patient has destructive cavitary tuberculosis before he realizes he is sick, a very common trick of Nature, the outlook changes profoundly. The prospect of confining the disease by rest treatment alone diminishes and there are many fatalities. Numerous studies bear this out, one of the latest by Refsum [1] being based on a period of observation of at least 18 years. Of 105 conservatively treated patients (without collapse of the lung) who had suffered from unilateral cavitary tuberculosis of the lung, 37 per cent were dead within three years, 63 per cent within six years, and 77 per cent within 12 years. For patients of such categories, surgery has often saved the day by collapsing and sealing up the cavities from which the infection might have kept spread-

* Presented at the Thirty-third Annual Session of The American College of Physicians, Cleveland, Ohio, April 24, 1952.

ing. In Refsum's series of 391 comparable cases treated by unilateral thoracoplasty, the mortality was reduced to 40 per cent of these figures at the end of the first 10 years. On the basis of this and other recent reports of long follow-up studies [2, 3, 4] covering a total of more than 1,200 cases, the modern thoracoplastic operation may be expected to save or greatly prolong the lives of 60 per cent or more of patients judged to be suitable for treatment by this procedure. A majority of those responding satisfactorily will experience an arrest of the disease, will be able to lead reasonably active lives, and, in many instances, to undertake full time work. These results may be anticipated in spite of the fact that the disease is left fundamentally unchanged except for the mechanical readjustment permitting more effective and durable healing.

Achieving the maximal benefits of thoracoplasty, or of any other procedure, depends greatly upon the proper selection of cases, due preparation by treatment prior to the operation, and adequate treatment postoperatively. This implies that complete diagnostic facilities should be available for the evaluation of each case, and all modern types of therapy should be accessible. Continuity of care is an asset throughout the course of the patient's illness and after recovery.

Whatever may be the procedure selected in a given case, it is predicated upon an understanding of the pathogenesis of tuberculosis and its operation in the specific situation in hand. Tuberculosis is chronic and prone to relapse, because the infection causes necrosis of tissue which does not slough out cleanly and in which the bacillus is likely to survive during many years, often for the duration of the life of the patient. While bacilli may die out after some years in lesions which are small in volume and in which necrosis is not extensive, the disease is almost always more advanced than this if treatment is required. Consequently, the planning of any regimen must be based upon the assumption that resolution of inflammatory exudate under the influence of chemotherapy or of rest alone will leave behind residual collections of necrotic or excavated tissue harboring living organisms. The problem then is to promote sufficient fibrosis to confine the infection within organized and encapsulated foci or in some cases, to eliminate these entirely.

Criteria have been established to permit a fairly accurate prognosis of the disease in its many manifestations. Small relatively clean cavities may heal naturally and permanently. Large cavities rarely do so except after some mechanical treatment. Large caseous lesions, even though controlled by rest and chemotherapy sufficiently to abolish all clinical symptoms, are very likely to undergo liquefaction and sloughing at some later period, leading to relapse. The local anatomic features are not the only determinants of the fate of the lesions, since they are also influenced strongly by the innate and acquired resistance of the host. In deciding upon the indications for and probable results of thoracic surgery, such basic concepts always have a bearing. The primary purpose should not be to save time in the immediate

future, although this usually is the patient's chief concern, but rather to bring the disease under such control that, after the necessary sacrifice of time, the chance of relapse will be minimized, and the prospect of the patient's returning to an active and useful life will be reasonably well assured.

Considering all these principles with reference to artificial collapse of the lung to control the disease, it may be said that the only close competitor of thoracoplasty is artificial pneumothorax. This of course was a predecessor of thoracoplasty, and it has the virtue of relative simplicity. Undoubtedly many lives have been saved by this procedure. As the scene changes, however, the practice of artificial pneumothorax in this country finds less favor than formerly, largely because it does not always suffice for its purpose and is attended by frequent and sometimes serious infections of the pleura. Happily, it is seldom necessary now to resort in desperation to artificial pneumothorax for the early control of acutely progressive pneumonic types of the disease, since chemotherapy can be depended upon more surely for this purpose. It is in cases of this type that the serious complications of pneumothorax, such as empyema and bronchopleural fistula, were met most often. This leaves subacute or chronic predominantly unilateral lesions without extensive destruction of tissue which may be successfully managed with pneumothorax if pleural adhesions do not prevent. In these cases, so treated, the risk of pleural infection is materially less. Nevertheless, the suitability of a number of these cases for surgical resection or thoracoplasty further narrows the field of pneumothorax treatment, which usually is maintained for from two to five years to be successful.

The minor surgical procedure of phrenic nerve interruption for paralysis of the diaphragm has reached a point approaching obsolescence. The mechanical effects are limited and seem to add very little to the benefits of rest treatment alone or in combination with specific drug therapy.

The declining practice of artificial pneumothorax has been concurrent with an increasing use of pneumoperitoneum, which is intended to raise the diaphragm, diminish its motion and impart a favorable mechanical influence upon the diseased lung. Sometimes, particularly in bilateral cases, it seems to be of material help in controlling the disease and in paving the way for surgery. It is always difficult to judge how much of the response should be credited to the pneumoperitoneum, how much to bed-rest, and how much to chemotherapy; certainly the benefits of the last two are more evident. Now that a number of specific drugs are coming into use, it is probably reasonable to anticipate that the future will witness a less frequent and more discriminating use of pneumoperitoneum.

A variety of plastic operations to collapse diseased parts of the lungs has been advocated and used in different clinics of the world. Extrapleural pneumothorax, created by stripping the parietal pleura from the chest wall through the plane of the endothoracic fascia, collapsing the lung manually and maintaining the space by refills of air, has been employed frequently,

particularly in a number of foreign clinics. In the clinics of the United States and of some other places, the operation now is not often used because of the hazard of infection, the difficulty of maintaining the space artificially, and the frequent necessity of making the collapse permanent by later thoracoplasty. Various substances, such as wax and plastic materials, have been used to fill the space and maintain the collapse, but these usually have been found to be objectionable foreign bodies when they are kept in place indefinitely.

Closed tube drainage with suction has sometimes been effective in draining and promoting the healing of pulmonary cavities where the natural bronchial drainage was inadequate. However, the effects of the procedure are unpredictable, infections of the chest wall and other disadvantages are encountered, and other surgical procedures often become necessary. The range of usefulness of this type of operation is very narrow and has given way almost entirely to the more predictable and effective operations of thoracoplasty or resection.

Resection of lobes or entire lungs was developed and perfected mainly for malignant and suppurative destructive lesions of the lung, including bronchiectasis. In time the operation became relatively safe and, with the use of antibiotics, complications were reduced to a point where the prospects of benefit far outweighed the hazards of the disease. In cases of tuberculosis of the lung or pleura, however, such operations were hazardous in a high degree, largely because of the chronic mixed infections which would supervene in the pleura, the persistence of sinuses of the chest wall and the frequency of spread of tuberculosis in the opposite lung. It was not until after the discovery and clinical use of streptomycin that pneumonectomy and lobectomy could be approached with any degree of assurance that the patient would escape these serious and often fatal complications. Now, in situations involving extensive caseous necrosis or cavitation of a lobe or a lung, resections sometimes may be carried out without serious additional loss of pulmonary function and with better promise of control of the disease than is afforded by other measures. Thoracoplasty is seldom adequate for complete closure of very large cavities involving most of one or more lobes, nor is it usually sufficient to prevent the sloughing of large caseous masses after the lung is collapsed. An uncertain percentage of these cases may be salvaged by surgical removal of the diseased lobes. Obviously, the limitations are rather narrow because disease of this extent in one lung inevitably is associated with spreads of recent or remote origin in the opposite lung. It is therefore necessary to determine either that the lesions of the opposite lung are of small extent and well arrested or that they may become so after a long period of treatment with chemotherapy and bed-rest. During this interlude a further advantage in preparation for resection may be gained by the diminution of exudate in and from the cavitary and necrotic lesions; the sputum is reduced and, in some cases, tubercle bacilli disappear from it

temporarily. Under these conditions the time is ripe for surgical resection, assuming that the general condition of the patient and the lack of other complications warrant it. Resection is carried out then while streptomycin and para-aminosalicylic acid or some other agents are still exerting their antimicrobial effect. The risk of a fresh spread to the opposite lung and of serious postoperative pleural infection is minimal, and likewise the danger of a postoperative bronchopleural fistula is reduced. As soon as possible thereafter, a partial or complete thoracoplasty is performed to help obliterate the vacant pleural space which, if successful, guards effectively against later pleural infection and mechanical displacement of the mediastinum. A modified approach for the elimination of chronically diseased and excavated lobes takes the form of simultaneous lobectomy and thoracoplasty. The early success of this has been impressive in well selected cases.[5, 6]

A type of pulmonary resection which promises to have wider application and more beneficial results is that designed for the removal of segments, cones, wedges or blocks of diseased tissue. The development and perfection of these procedures have been made possible by a better understanding of the segmental anatomy of the lung, the attainment by well trained thoracic surgeons of special skill in identifying these anatomic relationships at the operating table and in dissecting segments or their subdivisions cleanly and safely, and the important demonstration by Medlar [7, 8] of the pathologic nature of apparently arrested necrotic tuberculous lesions, their anatomic distribution and their connections with the bronchial tree. The operation is employed in cases in which well localized chronic necrotic lesions present a threat of future relapse. It is to be considered for patients in whom healing under bed-rest and specific treatment has brought about temporary arrest of lesions in such localized areas. This includes certain "minimal" lesions, particularly in young people in whom previous treatment has controlled the disease but has left small chronic foci from which bacilli are occasionally discharged, as shown by positive cultures or stained smears of the sputum or gastric contents. In either situation the resistance of the patient may be good and there may have been complete symptomatic recovery; nevertheless, the potentialities of future exacerbations may be great, and no other preventive of this can be foreseen except a prolonged and perhaps permanent limitation of the activities of life. This obviously is a particularly serious handicap for adolescent youths and young adults whose careers normally would lie ahead. Resection is therefore a possible alternative and, in many cases of this type, is the treatment of choice.

Selection of cases for such limited resections depends fundamentally on a judgment of the chronicity and potentialities of the lesions which must be based on proper preliminary treatment and observation. Lesions of a pneumonic character which are confined to one or several segments are first treated by bed-rest, usually with combined streptomycin and para-aminosalicylic acid therapy for a period of months, during which the inflammatory

pneumonic exudate may be expected to resolve. This leaves behind unchanging residuals which, by virtue of this quality, may be assumed to represent more or less solid necrotic foci which have not sloughed, or cavities, some of which may be more or less filled with inspissated exudate. In either event, these are the foci in which living bacilli are likely to persist and give rise to later exacerbations. Stabilization of the disease at this point is determined by the passing of at least several months during which little or no change is observed. The nature and localization of the residual lesions are further studied by various x-ray views, including tomograms, and the possibility of relapse is estimated according to individual circumstances, including the age of the patient, his probable resistance to the infection, and the demands which the future is likely to make upon his energies. Similarly, small lesions which previously had been treated by rest alone and which now show a tendency to relapse or to the discharge of tubercle bacilli should be judged in the light of the previous course of the disease. In some of these cases a repetition of rest and chemotherapy may promote permanent arrest but, in many, resection promises more lasting and certain effects.

The employment of segmental and wedge resection after various forms of preparatory treatment is just emerging from the stage of investigation. The results in different clinics vary somewhat,[9] and it is too early to judge the final outcome of most of these cases. In highly skilled hands, however, the success has been striking. Chamberlain[10] has performed wedge resections in 30 cases and segmental resections in 270. He states that 90 per cent of these patients have three or more negative cultures after a period of six months to four years. The mortality thus far has been 3 per cent; the operative mortality (within 60 days), 1 per cent. Bronchial fistulas requiring further surgery have occurred in 6 per cent of the cases. Among about 100 cases considered ideal for this type of operation there has been only one death. The procedure will undoubtedly find increasing favor for the types of cases mentioned above. However, the required technic is highly specialized, the need of preliminary treatment in capable hands is great, postoperative care and attention are of vital importance, and timing of the operation with reference to the extent and dynamics of the lesion is so crucial that the best results can be anticipated only in those clinics adapted for this kind of work. Under less exacting conditions, many avoidable accidents and complications probably would occur.

Following any surgical procedure, the need of after care should be based upon the presumption that tuberculous lesions still remain in the lungs and possibly elsewhere. Surgery is effective in helping to control and confine or remove the lesions, which are judged to represent the greatest threat and probable source of relapse under alternative conditions. Other lesions of small size which are not obviously fresh and active will very likely heal by natural mechanisms. Since the chief goal is not the immediate saving of time but rather the prevention of relapse and the saving of life, these patients

are kept on the rest cure after operation for periods of variable length, often six months to a year. Then, with gradual rehabilitation, the prospect of a lasting arrest of the disease is great.

Summary

Among the various surgical procedures available for the treatment of pulmonary tuberculosis, thoracoplasty and resection are the most effective and dependable. The latter is now developed to the point where diseased segments or lesser sections of the lung may be successfully removed.

The benefits of these procedures depend on a wise selection of cases, adequate preparatory treatment with rest and antimicrobial therapy, highly skilled surgical technic, attentive postoperative care, and further periods of rest after recovery from the operation.

In the approach to treatment the first goal is the attainment of recovery which will be permanent. The immediate saving of time is of secondary importance to the avoidance of relapse.

The progress of surgery and the availability of a number of specific drugs necessitate a reorientation of indications for various therapeutic procedures such as artificial pneumothorax and artificial pneumoperitoneum. The changes in progress are discussed.

BIBLIOGRAPHY

1. Refsum, E.: Thoracoplasty in the treatment of cavernous tuberculosis of the lung, Acta tuberc. Scandinav. Supplement 29, Copenhagen, 1951.
2. Adie, G. C., Childress, W. G., Brezing, H. J., and Taylor, D.: Late results in the treatment of pulmonary tuberculosis by thoracoplasty, J. Thoracic Surg. **23**: 92–96 (Jan.) 1952.
3. Lees, W. M., Yang, S. C. H., Papoulakos, M., Alexander, J., and Larralde, A.: Results in 278 patients who had the modern type of thoracoplasty for tuberculosis, J. Thoracic Surg. **22**: 329–340 (Oct.) 1951.
4. Douglass, R.: Personal communication.
5. Ellis, F. H., Jr., Clagett, O. T., and Carr, D. T.: Simultaneous pulmonary resection and thoracoplasty in the treatment of pulmonary tuberculosis, Am. Rev. Tuberc. **65**: 159–166 (Feb.) 1952.
6. Conklin, W. S., Tuhy, J. E., and Grismer, J. T.: Thoracoplasty combined with resection for pulmonary tuberculosis, J. Thoracic Surg. **22**: 271–294 (Sept.) 1951.
7. Ryan, B. J., Medlar, E. M., and Welles, E. S.: Simple excision in the treatment of pulmonary tuberculosis, J. Thoracic Surg. **23**: 327–340 (April) 1952.
8. Medlar, E. M.: Pathogenetic concepts of tuberculosis, Am. J. Med. **9**: 611–622, 1950.
9. Overholt, R. H., Wilson, N. J., and Gehrig, L. J.: The place of pulmonary resection in the treatment of tuberculosis, Dis. Chest **21**: 32–50 (Jan.) 1952.
10. Chamberlain, J. M.: Personal communication.

THE DIAGNOSIS AND MANAGEMENT OF ASYMPTOMATIC ISOLATED INTRATHORACIC NODULES *

By SIDNEY E. WOLPAW, M.D., F.A.C.P., *Cleveland, Ohio*

MASS chest x-ray surveys, originally intended to detect early pulmonary tuberculosis, have also revealed that other intrathoracic lesions may be found with some degree of frequency in apparently healthy people. Particularly significant is the knowledge, now commonplace among chest physicians and thoracic surgeons, that in their early development many of these lesions are silent, the patient entirely unaware of their existence because symptoms are lacking. Even the most adept diagnostician is often unable to elicit their presence by the ordinary methods of physical examination.

A varied assortment of symptomless intrathoracic conditions has been discovered in this manner. In this group are the isolated well defined nodules, often of small size, which may offer considerable difficulty in diagnosis and therapy. Should these nodules happen to be inflammatory in origin, or benign tumors, there is usually no urgency concerning their proper recognition and treatment. On the other hand, should they represent a phase in the early development of a carcinoma, then incorrect diagnosis and improper management may prove disastrous to the patient.

We shall concern ourselves with three problems:

1. The significance of asymptomatic isolated nodules.
2. The diagnostic methods available for their clinical evaluation.
3. The proper therapeutic management of nodules discovered by routine x-ray examination; in particular, the justification for recommending major surgical procedures for these silent lesions in apparently normal individuals.

THE SIGNIFICANCE OF ASYMPTOMATIC NODULES

In a patient who considers himself to be healthy, the discovery of an abnormality by routine chest x-ray examination usually arouses a mixture of shock, fear and disbelief, especially if he is informed that a malignant tumor may be present. Indeed, among physicians who have had little contact with this problem, and whose concepts of disease are still based upon the presence of traditional signs and symptoms, many are reluctant to accept the idea that such asymptomatic lesions can really be significant. If they are told further that these silent and often innocent appearing nodules require early surgical intervention despite the absence of a specific diagnosis, it may

* Presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 22, 1952.

From the Departments of Medicine, Cleveland City and Mt. Sinai Hospitals, and the Western Reserve University School of Medicine.

be necessary to overcome their natural desire to observe the course and development of the lesions before accepting the surgical decision.

However, a few experiences illustrated by the following cases will usually convince even the most skeptical that routine chest x-ray examination provides a unique opportunity for the accurate detection of early intrathoracic

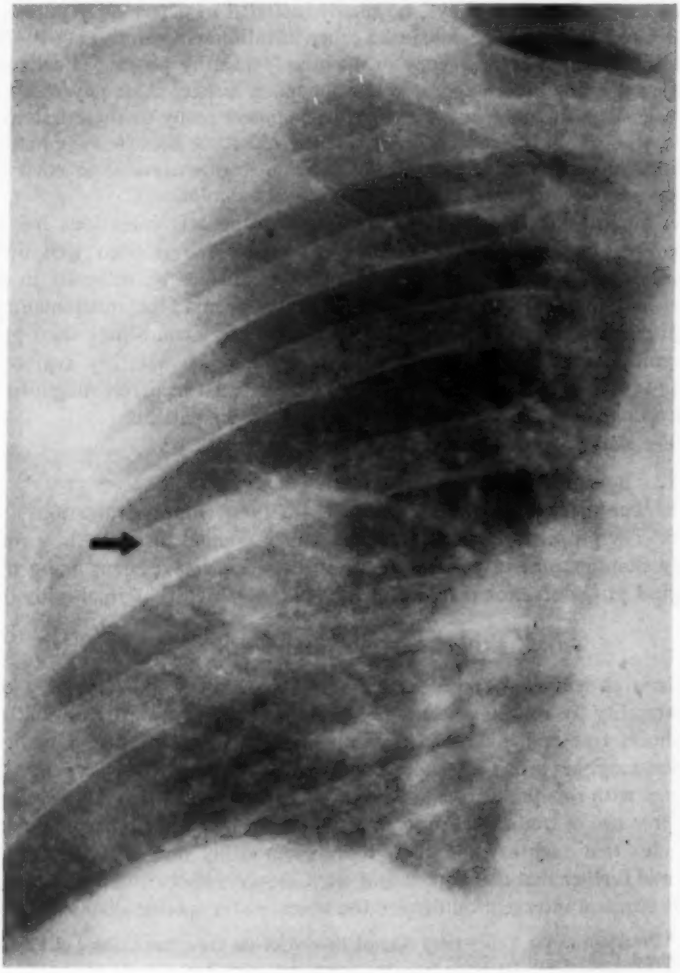


FIG. 1. *Case 1.* Asymptomatic nodule in right lower lobe. Pathologic diagnosis: adenocarcinoma of the bronchus.

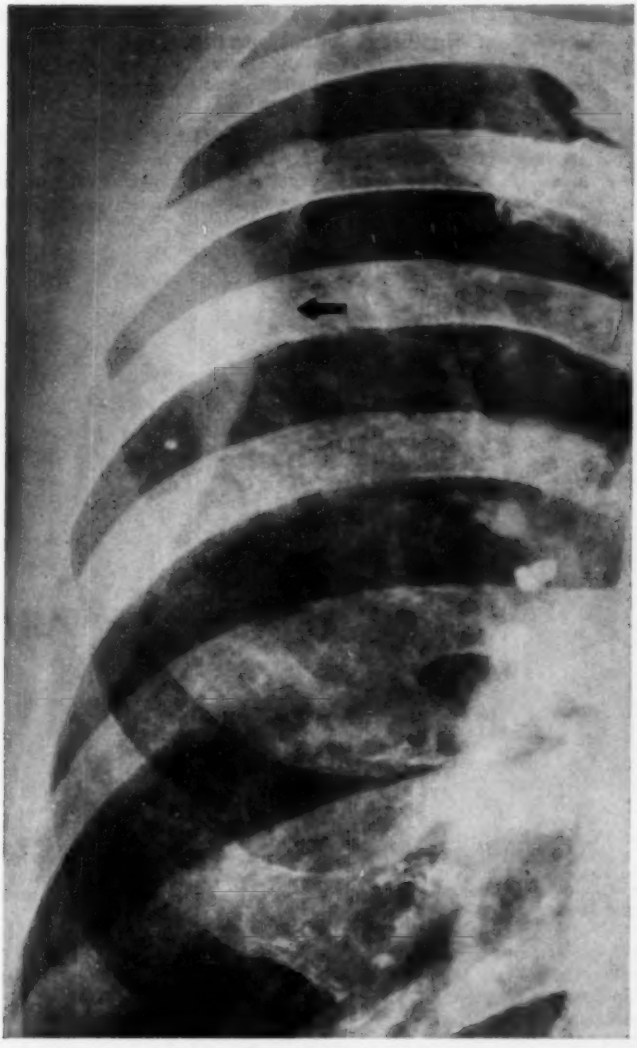
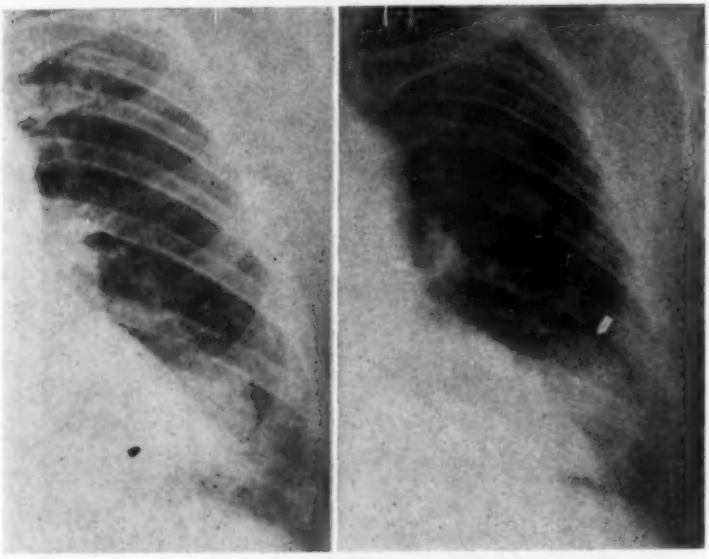


FIG. 2. *Case 2.* Nodule in peripheral portion of the right second anterior interspace. The patient was admitted because of a left lower lobar pneumonia. Pathologic diagnosis: squamous cell bronchogenic carcinoma.

disease, and that the nodules which are discovered in supposedly normal people may represent significant lesions, particularly bronchogenic carcinomas.

Case Reports

Case 1 (figure 1). During the course of a survey late in September, 1948, a 48 year old attorney had a chest film which showed a circumscribed nodule in the right lower lobe. He was completely asymptomatic, and physical examination was negative. Gastrointestinal series, colon studies and intravenous pyelography were



A B

Fig. 3A. *Case 3.* Nodule in left lower lobe, April, 1945. The lesion was detected during a general physical examination. No recommendation for further treatment or observation was made.

Fig. 3B. *Case 3.* Enlargement of nodule noted in survey chest film, August, 1949. Pathologic diagnosis: hamartoma.

negative, except for a rectal polyp which was removed and proved to be benign. Tuberculin skin test was positive; coccidioidin and histoplasmin skin tests were negative. Sputum examination did not reveal tubercle bacilli.

Inasmuch as a primary bronchogenic carcinoma could not be excluded, exploratory thoracotomy was decided upon despite the absence of all symptoms and signs, and the inability to establish a preoperative diagnosis. A firm nodule was found which frozen section revealed to be carcinoma. Pneumonectomy was done (Dr. S. O. Freedlander). Histologically, this was an adenocarcinoma with bronchopulmonary and paratracheal lymph node metastases. Postoperative recovery was uneventful, but death occurred nine months later from a cerebral metastasis.

Case 2 (figure 2). A 68 year old white male was hospitalized in April, 1949, with a left lower lobe pneumonia. He was critically ill but finally recovered with antibiotic treatment. His chest x-ray, however, showed a small, fairly dense nodule in the right second interspace. Physical examination, gastrointestinal x-ray ex-

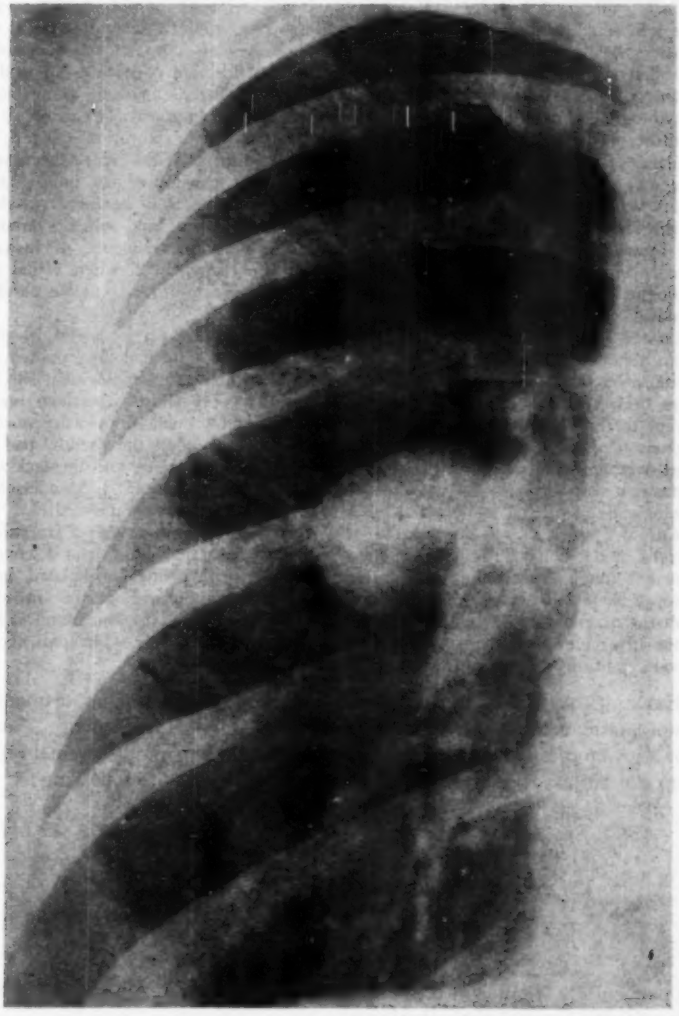


FIG. 4. *Case 4.* Asymptomatic nodule adjacent to right hilum, which had enlarged very slightly over a period of 10 years. Pathologic diagnosis: fibroma of lung.

amination, intravenous pyelography, bronchoscopy and bacteriologic and cytologic studies all failed to establish the character of the nodule. It enlarged during his convalescence and in July, 1949, when his condition permitted, the nodule was extirpated (Dr. H. J. Mendelsohn). It proved to be a squamous cell carcinoma. The patient died from a pulmonary embolus on the second postoperative day.

Case 3 (figure 3 A, B). A 56 year old white female was found to have a nodule in the left lung during a survey in 1949. She was asymptomatic and physical examination was negative. A previous chest film elsewhere in 1945 had shown a similar but smaller shadow which apparently had not aroused concern. All studies, including search for a primary neoplasm, skin tests, bronchoscopy and bacteriologic and cytologic examination failed to establish a definitive diagnosis. Because of enlargement of the nodule operation was recommended. At exploration (Dr. S. O. Freedlander), a firm mass was found in the anterior portion of the interlobar fissure. There was no evidence of lymph node involvement or invasion of the lung. Local excision was accomplished. The pathologic diagnosis was that of hamartoma, which was grossly well encapsulated, was not in pulmonary tissue, and which contained adult bronchial elements. There was, however, microscopic evidence of invasion of the capsule. The patient remained well until February, 1952, when visual and neurologic symptoms developed. She is under observation for a possible cerebral metastasis.

Case 4 (figure 4). A 59 year old white female had known for about 10 years that an abnormal shadow was present in the right lung. She had never noted any symptoms, but in jobs where a chest film was a prerequisite for employment she had always been rejected. X-ray examination showed a very sharply outlined nodule adjacent to the right hilum. Physical examination and bronchoscopy were normal. Comparison of x-ray films suggested that slight enlargement of the shadow had occurred over a period of years. Despite the absence of symptoms and the lack of a diagnosis, it was recommended that the nodule be removed (Dr. H. J. Mendelsohn). Pathologically it proved to be a fibroma. Her convalescence was uneventful.

Case 5 (figure 5). A 40 year old colored male was admitted with a fracture of the right ulna. During his hospital course an asymptomatic nodule was discovered in the left lung. Tuberculin was positive. Search for a primary neoplasm, bronchoscopy, bacteriologic and cytologic examination and angiocardiography failed to establish a diagnosis. The nodule was excised (Dr. M. Reydman) and found to be a caseous tuberculous mass containing innumerable tubercle bacilli. The patient was in good condition three months after operation.

Examples such as these represent only part of a varied assortment of asymptomatic intrathoracic lesions which have been operated upon.[1] Analysis of a group of 25 silent circumscribed nodules in apparently normal people whom the author has observed in recent years reveals the following: *

Bronchogenic carcinoma	6
Tuberculoma	7
Bronchial adenoma	2
Hamartoma	2
Metastatic carcinoma	2
Fibroma	1
Pericardial cyst	1
Arteriovenous aneurysm	1
Granuloma, etiology undetermined	3

It is particularly significant that of the entire group six (25 per cent) proved to be primary bronchogenic carcinoma.

* These patients were observed on the Chest Services of the Cleveland City, Mt. Sinai and Crile Veterans Administration Hospitals, and the County Tuberculosis Clinic.

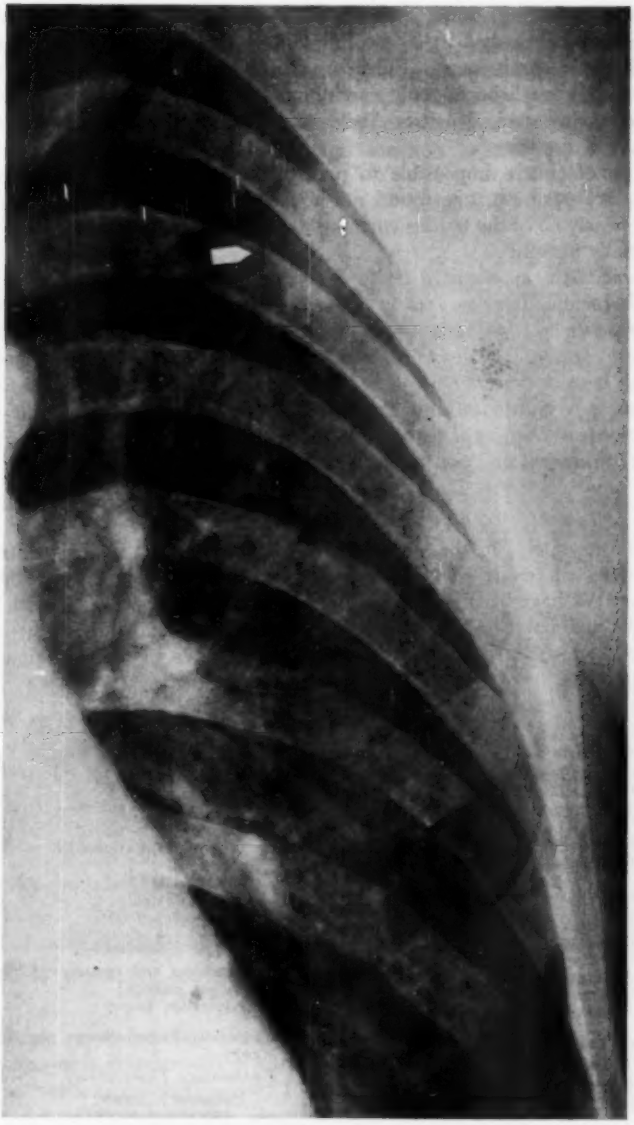


FIG. 5. *Case 5.* Nodule in peripheral portion of left first anterior interspace. Pathologic diagnosis: fibrocaseous tuberculosis.

Similar findings have been noted by many others. Thus, O'Brien, Tuttle and Ferkaney [2] in 21 "coin" lesions found that 38 per cent were bronchogenic carcinomas. Effler [3] in 16 "solitary lung tumors" reported six which were bronchogenic carcinoma. In 21 cases of single, circumscribed intrathoracic densities Abeles and Ehrlich [4] found five primary carcinomas of the lung.

It is of course impossible to predict the eventual fate of the nodules which, at operation, are found not to represent malignant tumors. Certainly nearly all of the lesions encountered in the author's experience could be potentially harmful.

Hence, it is emphasized that the existence of isolated well circumscribed intrathoracic nodules on routine x-ray examination of the chest may indicate the presence of significant disease. In particular, the possibility that the lesions represent an early phase in the development of bronchogenic carcinoma is to be considered. The asymptomatic character of the nodule, the absence of physical signs and the apparent state of good health of the patient must not lead the physician to the false conclusion that the abnormality cannot be significant and that it therefore does not require treatment.

Differential Diagnosis

Unfortunately, in the stage in which circumscribed nodules often have been detected, exact diagnosis has rarely been possible despite intensive study. We have been unable to formulate any definite criteria which can be considered reliable in differential diagnosis. The following table lists the methods which have been utilized at various times in the investigation of such patients.

Diagnostic Methods

1. *Clinical History*
   - Occupational data
   - Geographic data
   - Tuberculosis contact
2. *Physical Examination*
   - Extrapulmonary lesions
3. *Roentgenologic Examination*
   - Fluoroscopy
   - Laminagraphy
   - Bronchography
   - Angiography
   - System review
   - Serial observations
4. *Skin Testing*
   - Tuberculin
   - Histoplasmin
   - Coccidioidin
5. *Bronchoscopic Examination*
   - Bronchial aspiration
6. *Laboratory Examinations*
   - Sputum—TB, fungi
   - Gastric aspiration—TB and fungus culture
   - Blood counts and chemistry
   - Serologic studies
   - Agglutination tests
7. *Pathologic Examinations*
   - Bronchial and sputum cytology
   - Biopsy material
   - Aspiration biopsy
8. *Diagnostic Pneumothorax and Thoracoscopy*
9. *Exploratory Thoracotomy*
   - Pulmonary biopsy

Few of these methods short of exploratory thoracotomy have been of any genuine help in differential diagnosis. The clinical history and physical

examination are usually not significant. The age and sex of the patient may suggest certain diagnostic probabilities but cannot conclusively establish a specific diagnosis or exclude the presence of a malignant lesion. Skin tests, whether negative or positive, cannot differentiate between granuloma and tumor. Bronchoscopy has seldom been of aid because of the small size of the nodules and their frequent peripheral location beyond the range of

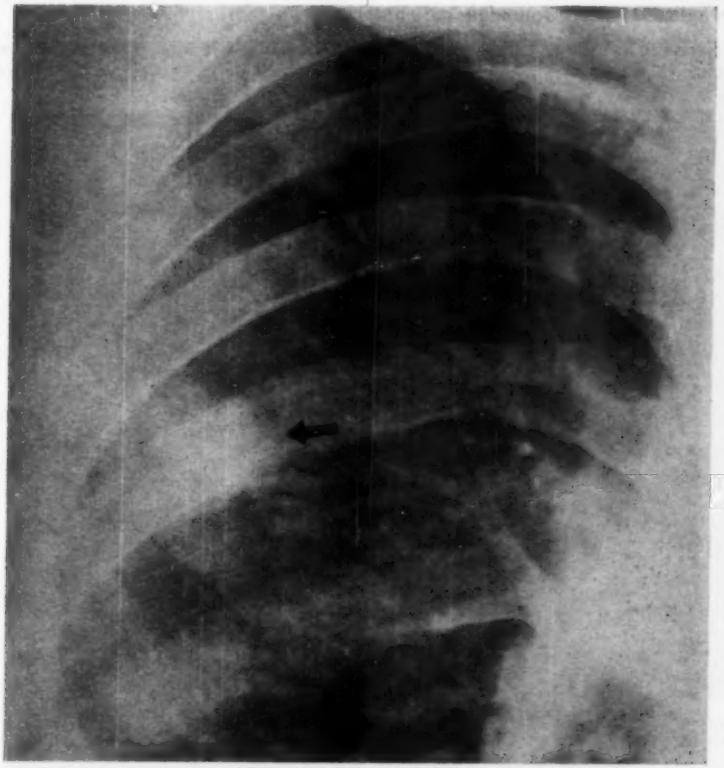


FIG. 6. *Case 6.* One and one-half cm. nodule in right third anterior interspace. Pathologic diagnosis: undifferentiated bronchogenic carcinoma.

bronchoscopic visualization. Bacteriologic examination of sputum and gastric material is infrequently positive for tubercle bacilli or fungi. There is little justification in lengthy delay for cultural studies, guinea pig inoculation or repeated examinations. Aspiration biopsy of nodules as small as those demonstrated is difficult and not without considerable risk. It has been abandoned as a diagnostic measure.

Sputum and bronchial aspiration cytology may be diagnostic if tumor cells are found, but this has not been a frequent finding in our experience. In this group, even repeated negative examinations cannot be relied upon to exclude the possibility that a malignant tumor exists.

It has also been impossible to establish any roentgenologic criteria which will permit adequate differentiation of these nodules. A variety of pathologic conditions may simulate each other closely in size, definition and density, as indicated by the following patients:

Case 6 (figure 6). A 69 year old white male had a routine x-ray of the chest during the Greater Cleveland survey in 1949. A small 1.5 cm. nodule was discovered

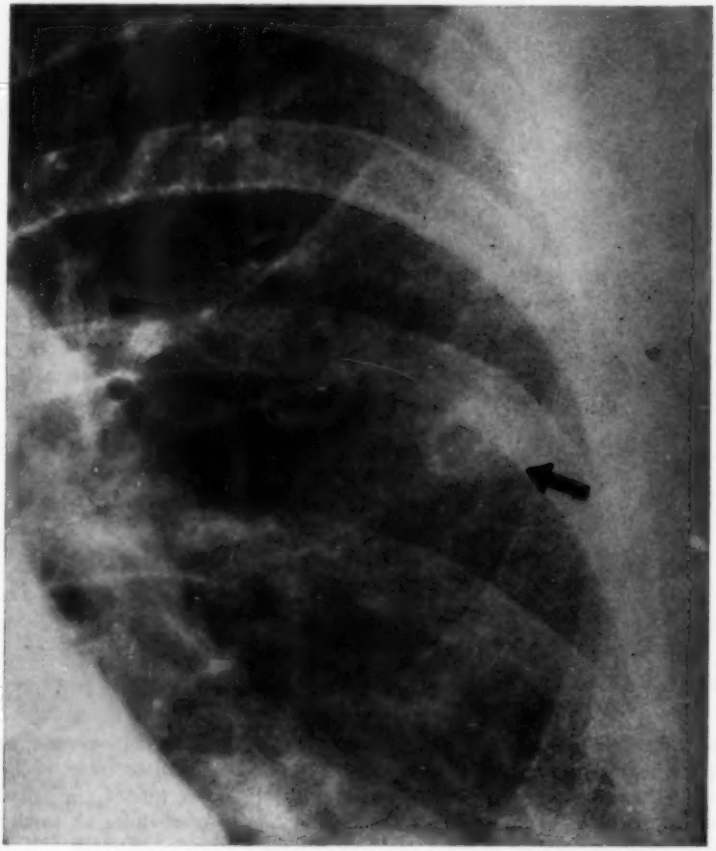


FIG. 7. *Case 7.* One cm. nodule in left fourth anterior interspace. Pathologic diagnosis: fibrocaseous tuberculosis.

in the right lung. He was asymptomatic and there were no abnormal physical signs. Chest films made in 1945 and 1948 were reviewed and found to be normal. No specific diagnosis was possible despite search for a primary tumor, skin tests, bronchoscopy, and bacteriologic and cytologic studies. In October, 1949, at exploratory operation (Dr. H. J. Mendelsohn), there was found an undifferentiated carcinoma, for which pneumonectomy was performed. In January, 1952, the patient appeared in good health without evidence of metastases.

Case 7 (figure 7). A 46 year old white female was admitted in May, 1949, for a fractured leg. Routine x-ray examination revealed a small circumscribed nodule in

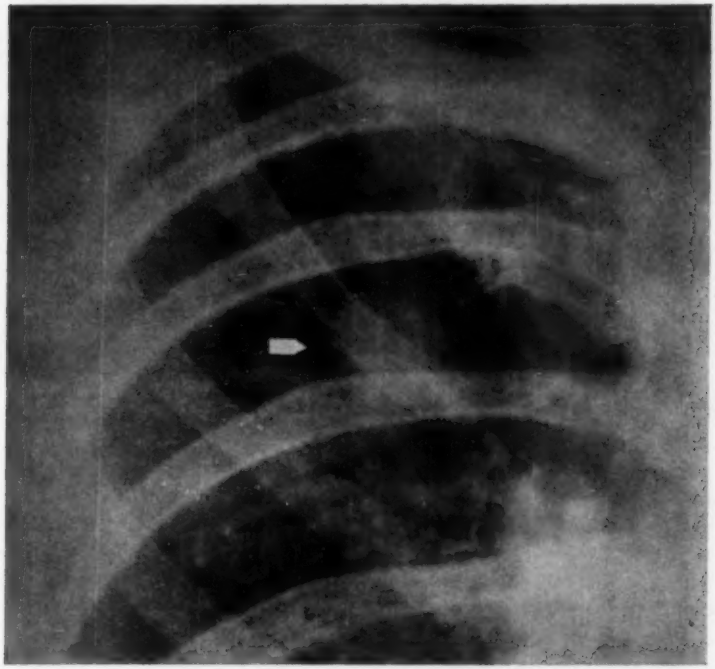


FIG. 8. *Case 8.* One and one-half cm. nodule in the right first anterior interspace. The nodule enlarged slowly over a period of seven years. Pathologic diagnosis: benign bronchial adenoma.

the left lung which was not present on a film one year earlier. There were no pulmonary signs or symptoms. All other studies failed to establish a diagnosis. Because of the inability to determine the character of the nodule and the knowledge that it was not present previously, surgery was recommended. The density proved to be a small fibrocaseous tuberculous lesion for which local resection sufficed (Dr. M. Reydman). Convalescence was uneventful.

Case 8 (figure 8). A 42 year old white female was known to have a small nodule in the right upper lobe in 1939 during a routine examination. The nodule increased

slowly in size but no therapy was recommended, because she was asymptomatic and there were no abnormal clinical findings. Bronchoscopy and repeated sputum studies were negative. In December, 1946, because of a hemoptysis and further enlargement of the nodule, it was removed (Dr. S. O. Freedlander). Histologically, the lesion was a benign bronchial adenoma. The patient has remained well.

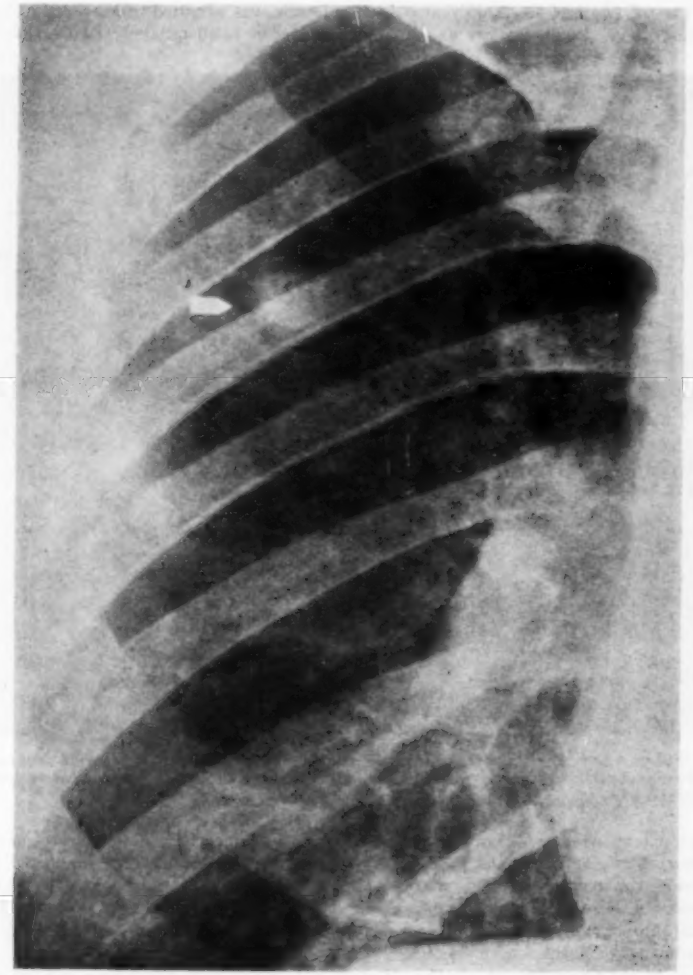


FIG. 9A. *Case 9.* Nodule in right second anterior interspace.

FIG. 9B. *Case 9.* Laminagram reveals a central core of calcification. Tuberculin positive, histoplasmin and coccidioidin skin tests negative. Diagnosis: tuberculoma.

Occasionally, angiocardiography has visualized an arteriovenous aneurysm. The only other x-ray finding which we believe may be of some practical value is the laminagraphic demonstration of a central core of calcification indicative of a tuberculous or histoplasmic lesion. Several nodules of this type have been observed without change over a period of years. In some cases certain benign tumors such as hamartomas and chondromas may also show small foci of calcification.

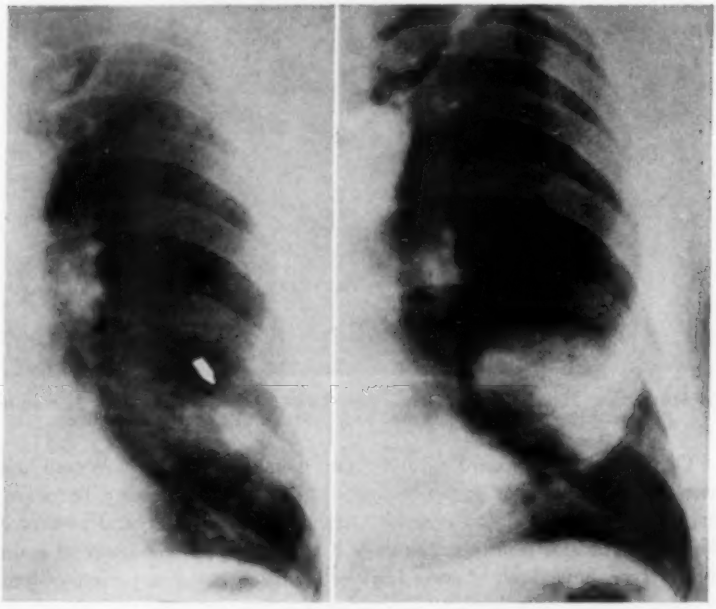
Case 9 (figure 9 A, B). A 46 year old white male was noted to have a small, well defined nodule in a routine survey film. He was asymptomatic, and physical examination was not helpful. Tuberculin was positive; histoplasmin and coccidioidin were negative. Laminagrams revealed a central core of calcium in the nodule. It was considered to be a calcified tuberculous focus. No further findings have developed over a three year period of observation.

Hence, it is emphasized that no satisfactory criteria exist for the exact differentiation of the variety of lesions which appears as isolated nodules. Even intensive investigation with many diagnostic procedures may fail to establish a specific etiology. In particular, there are no reliable methods which can exclude the presence of a malignant growth. The diagnostic

methods which are utilized should be applied promptly in order to avoid delay in therapy.

Management of Asymptomatic Nodules

Unless a specific diagnosis can be established, there is often great reluctance on the part of physicians to recommend treatment for silent, isolated nodules in apparently normal people. The attitude so frequently adopted is that if a lesion is asymptomatic, not detectable by physical signs and dis-



A B

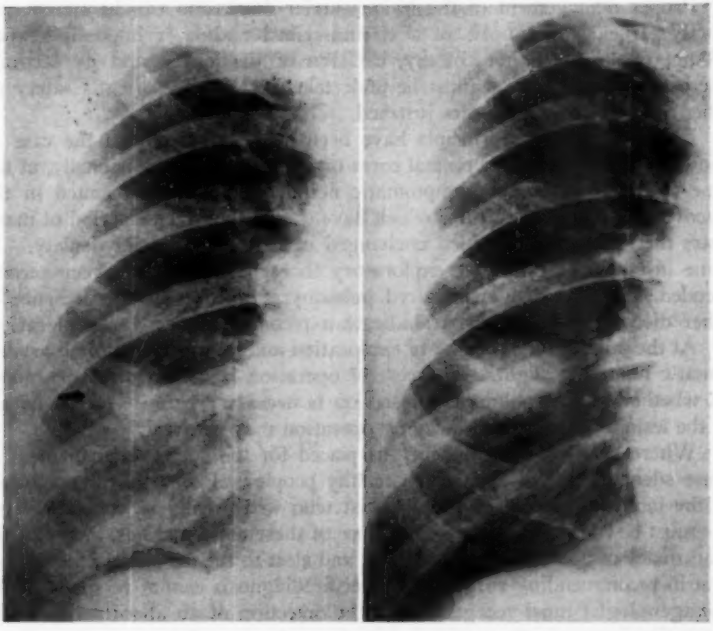
Fig. 10A. *Case 10.* Nodule in left lower lobe, April, 1949, erroneously interpreted as a calcification. No recommendation for further observation.

Fig. 10B. *Case 10.* Marked enlargement of nodule, August, 1950. The only symptom at this time was slight pain in the right shoulder and right costal margin. Pathologic diagnosis: adenocarcinoma of the bronchus.

covered only on routine x-ray examination, it is probably not significant. It is, however, well known that malignant tumors may remain unchanged in size and shape for prolonged periods. Too often a recommendation is made for periodic x-ray observation, during which time nodules may increase in size, or signs and symptoms intervene. With the knowledge that many of these lesions may be malignant, the decision to observe their development should be made only with a full realization of the possible consequences. In

inflammatory lesions or benign tumors no harm may ensue. However, to watch a malignant growth increase in size under observation may be dangerous to the patient and embarrassing to the physician. During such a waiting period metastases may occur or an operable lesion become inoperable. The danger of incorrect diagnosis and delay is illustrated in the following instances:

Case 10 (figure 10 A, B). A 59 year old white male was examined during a routine survey in April, 1949. A small nodule noted in the lower portion of the left lung was interpreted as a pulmonary calcification. No further studies were requested. In August, 1950, because of pain in the right shoulder and along the right costal margin, another chest film was obtained. There was now present a large mass at the site of the original nodule. Exploratory thoracotomy was carried out in September, 1950, and a pneumonectomy was performed (Dr. E. B. Kay). The mass proved to be an adenocarcinoma of the bronchus. Death occurred a few months later from widespread metastases.



A B

FIG. 11A. *Case 11.* Small nodule in right lower lobe, October, 1950. Despite a request for further examination the patient did not return until April, 1951, at which time a slight increase in the size of the nodule was apparent. Although the patient's physician had received notification of the change, a recommendation for treatment was not made until an x-ray of November, 1951, showed further enlargement of the nodule.

FIG. 11B. *Case 11.* Enlargement of nodule, November, 1951. Pathologic diagnosis: adenocarcinoma of bronchus.

In this case, incorrect interpretation of the original x-ray film led to a delay of 17 months in the treatment of a malignant tumor, which might originally have been curable.

Case 11 (figure 11 A, B). A 64 year old white male was found during a survey in October, 1950, to have a small faint density in the right lung. He was asked to return for further study but did not appear until April, 1951. The nodule had increased in size. At this time he was still asymptomatic and examination was negative. He was referred to his family physician, but no other measures were undertaken until a chest x-ray in November, 1951, revealed still further enlargement of the nodule. In December, 1951, exploration was performed (Dr. C. W. Munz), revealing an adenocarcinoma of the bronchus for which right lower and middle lobectomy were done. There was no evidence of lymph node metastases.

Again, an unfortunate delay of 14 months occurred in the treatment of a bronchogenic carcinoma. The tumor was resectable, but curability remains to be determined.

Proper management of the lesions under discussion can be stated succinctly: If exact diagnosis of a circumscribed nodule is impossible, then prompt exploratory thoracotomy, excision of the lesion, and its accurate microscopic identification must be undertaken. For the patient's safety no other course of action appears justified.

Exceptions to this principle have been made, especially in the case of nodules with laminated or central cores of calcification. Occasionally, at the time of detection of an asymptomatic nodule, inquiry has resulted in the discovery of earlier chest films which have shown that over a period of many years the lesion has remained unchanged in size, definition or density. In some instances of this type, exploratory thoracotomy has not been recommended. Advanced age, impaired pulmonary function or the presence of other diseases may also contraindicate a recommendation for exploration.

At the present time the risk of exploration and local excision of an asymptomatic nodule is slight. The risk of operation is usually then dependent on whether further pulmonary resection is necessary because of the nature of the lesion. The risk in delaying operation may be great.

Where shall the responsibility be placed for the correct management of these silent lesions of apparently healthy people? Primarily, in the hands of the family physician or the internist who will usually be consulted first. He must be cognizant of the significance of these abnormalities, aware of the inadequacy of our diagnostic methods, and alert to the danger of procrastination in recommending surgery if a specific diagnosis cannot be made. The roentgenologist must recognize that the detection of an abnormality in the x-ray film is merely the initial step in the evaluation of the patient, and that x-ray observation is not a substitute for microscopic examination of the lesion. The thoracic surgeon has the responsibility for the choice of procedure which will best serve the interests of the patient.

With few exceptions, asymptomatic isolated intrathoracic nodules are correctly treated only with prompt surgical exploration if an exact preopera-

tive diagnosis is impossible, or if the presence of a malignant tumor cannot be excluded with certainty.

Summary

Isolated circumscribed nodules are significant, since they may represent an asymptomatic phase in the development of intrathoracic disease, particularly bronchogenic carcinoma. Specific diagnosis may be impossible despite intensive clinical and roëntgenologic investigation. In the absence of an exact diagnosis, or the ability to exclude a malignant growth, exploratory thoracotomy for identification of the lesion is the only justifiable procedure.

BIBLIOGRAPHY

1. Freedlander, S. O., Wolpaw, S. E., and Mendelsohn, H. J.: Surgical experience with asymptomatic intrathoracic growths, Radiology **55**: 700, 1950.
2. O'Brien, E. J., Tuttle, W. M., and Ferkaney, J. E.: The management of the pulmonary "coin" lesion, S. Clin. North America **28**: 1313, 1948.
3. Effler, D. B.: Solitary lung tumors, Am. Rev. Tuberc. **63**: 252, 1951.
4. Abeles, H., and Ehrlich, D.: Single, circumscribed, intrathoracic densities, New England J. Med. **244**: 85, 1951.

CHANGES IN CONNECTIVE TISSUE REACTION INDUCED BY CORTISONE *

By R. H. Ebert and W. R. Barclay, *Chicago, Illinois*

Cortisone and adrenocorticotropic hormone (ACTH) have a profound effect on a variety of inflammatory reactions, including acute and chronic infections,[1, 2] wound healing,[3] the Shwartzman phenomenon,[4] chemical irritation [5] and thermal burns.[6] In an effort to elucidate the nature of the changes which occur during cortisone therapy, a series of in vivo studies was undertaken using the rabbit ear chamber technic. Since earlier work in this laboratory using the rabbit ear chamber technic as an in vivo method of observation had provided insight into the dynamics of certain inflammatory reactions and hypersensitive states, it was felt that a study of the effect of cortisone on these reactions might provide basic information as to how this hormone modifies the inflammatory response.

The rabbit ear chamber first described by Sandison [7] provides a thin layer of living vascularized connective tissue which can be observed by direct microscopy under all magnifications. It offers the major advantage of allowing the investigator to record serial in vivo changes in the same preparation over a period of weeks or months. It has the disadvantage of being a laborious method which does not permit large numbers of experiments.

Methods and Materials

The rabbit ear chamber as modified by Ahern, Barclay and Ebert [8] consists of a base plate one inch in diameter, a clear mica cover-slip, and a cover-slip supporting ring. The base plate and cover-slip supporting ring are made of Plexiglas. A circular table one-quarter inch in diameter projects upward from the center of the base plate, and there are three pegs at the periphery of the base plate which support the cover-slip and plastic ring.

The chamber is inserted in the pinna of the rabbit, using careful aseptic technic. Four holes are punched through the pinna with a special punch, a central hole one-quarter inch in diameter and three smaller peripheral holes. The skin is then carefully dissected back on both sides of the ear over an area the size of the chamber and the freed skin is cut away. Care is taken to leave the vessels intact. On completing the dissection the base plate is fitted on one side of the ear so that the central table projects through the central hole and the pegs project through the peripheral holes. The mica cover-slip and supporting ring are then fitted on the opposite side of the ear and the supporting ring is cemented to the pegs. A thin layer of

* Presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 24, 1952.

From the Department of Medicine, University of Chicago.

The work was sponsored from a grant from the United States Public Health Service.

clot 30 to 50μ thick is left between the table and the cover-slip, and new vessels and connective tissue grow into this area. The thin area over the observation table becomes vascularized in four to six weeks and develops a "mature" vascular pattern [9] with well differentiated arteries, venules and capillaries. All observations are made on this thin transparent layer of tissue one-quarter inch in diameter. Figure 1 shows the entire central table under 18 X magnification. A central plug made of silver projects through the middle of the observations table (the circular dark area in the center of

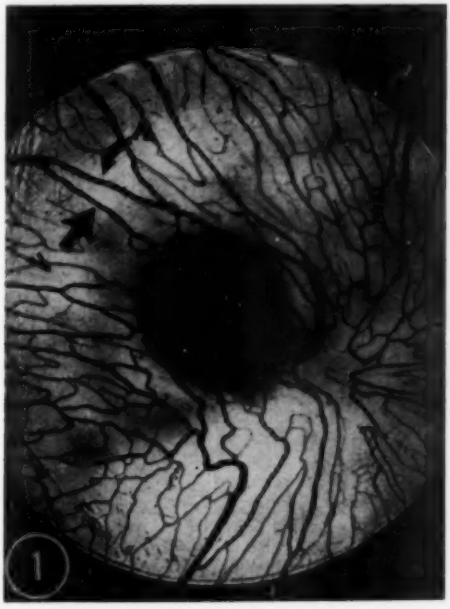


FIG. 1. Appearance of tissue on central table of ear chamber prior to administration of cortisone. There is moderate dilatation of artery (A) adjacent to venule (V). 18×.

figure 1). This can be removed after the tissue is mature, and the observation area can be inoculated directly.

Observations are made with a Bausch and Lomb research microscope fitted with a special movable stage which holds the chamber securely. The animal is tied to a specially constructed rabbit board, and all observations are made on the unanesthetized rabbit. A Bausch and Lomb spherical lamp is used for illumination, and a water filter is used to avoid heating the tissue. Photomicrographs are made with a Leica micro-attachment, and Kodachrome motion pictures are taken with an Eastman Kodak special camera.

All animals used in the experiments on tuberculosis infection were sensitized with BCG prior to inoculation. Chambers were infected with approximately 0.001 to 0.002 mg. (wet weight) of Ravenel RV freshly ground and suspended in saline. Tubercle bacilli were grown on Proskauer and Beck media. Old tuberculin (Lilly), suitably diluted with sterile saline, was used to produce the focal reaction. Pontamine sky blue (5 c.c. of a 5 per cent solution) and vital new red (10 c.c. of a 2 per cent solution) were used for intravitam staining in several experiments.[10] These dyes,

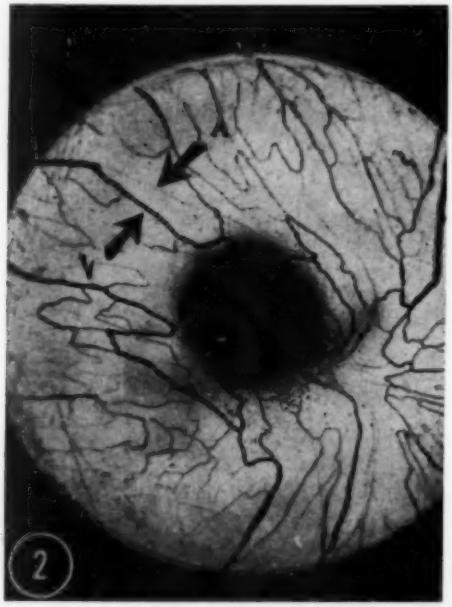


FIG. 2. The same chamber after 18 days of cortisone therapy (5 mg. daily). There has been an increase in the tone of the arteriole (A) so that it is barely visible at this power.

given intravenously, produce staining of macrophages and histiocytes in vivo and in these amounts produce approximately equivalent staining. Cortisone (Cortone, Merck) was given by intramuscular injections in doses ranging from 5 to 25 mg. once daily, as indicated in the text.

RESULTS

The effects of cortisone have been studied in a number of different types of reactions in the rabbit ear chamber. The modification of nonspecific inflammatory reactions has been observed as well as the effect of the hor-

mone on the apparently normal chamber. Tuberculous infection and the focal reaction in tuberculosis have been studied as examples of bacterial allergy, and serum sickness has been induced as a method of studying a type of anaphylactic hypersensitivity.

Nonspecific Inflammatory Reactions: At times, nonspecific inflammation occurs in the rabbit ear chamber. It is not always possible to determine the cause, but often it is produced by low grade infection of the tissue adjacent to the observation table. Such inflammation is characterized by vascular dilatation and sticking of white blood cells to vascular endothelium.

FIG. 3. A higher power view of the arteriole (A) shown in figure 1 and an adjacent venule (V). Note the diameter of the arteriole and the localized dilatations and constrictions. 100×.

Arterioles often show localized dilatations and constrictions similar to those seen in serum sickness,[11] and arteriolar sticking may be present. If the inflammation is very marked, there may be spectacular dilatation of venules so that the vessels have the appearance of sinusoids.

The effect of cortisone on such nonspecific inflammatory reactions was determined in eight animals. Three of these animals had chambers in both ears, so that observations were made on a total of 11 chambers. Seven animals received 10 mg. of cortisone daily for periods of from four to seven days (the average being seven days), and one animal received 5 mg. daily

for eight days. Two animals were given pontamine sky blue intravenously three days prior to cortisone. After four days of cortisone treatment these two animals received vital new red intravenously, and hormone treatment was continued for three days after administering vital new red. One animal received pontamine blue after four days of cortisone therapy.

The effects of cortisone were identical in every experiment. Vascular tone increased (figures 1 to 4), and there was a reduction in sticking of leukocytes to vascular endothelium. Sticking of leukocytes to arteriolar endothelium disappeared entirely, but venule sticking was variable and did

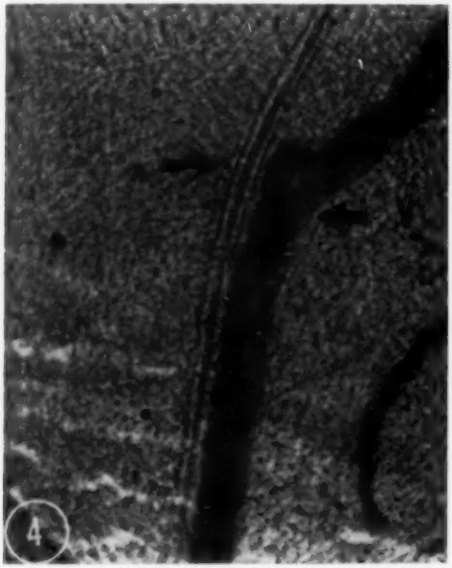


FIG. 4. The same arteriole shown in figure 3 after 18 days of cortisone. (This is a higher power of the arteriole barely visible in figure 2.) There has been considerable increase in tone.

not always disappear. These effects became apparent after three days of therapy, and the suppression of the inflammatory response was maximal after six to seven days.

The two animals receiving pontamine sky blue prior to cortisone therapy showed moderate staining of macrophages and histiocytes three days after the dye had been given. The same animals showed much less staining with vital new red given during cortisone therapy. Staining with these two dyes will occur even in the normal chamber, but the amount of staining is increased when the tissue is inflamed. The relative decrease in staining

during cortisone is further evidence for reduction in the inflammatory response.

The animal receiving pontamine sky blue during cortisone therapy showed minimal staining. A large abscess was present on the observation table, and prior to cortisone therapy the remaining tissue was markedly inflamed with sinusoidal dilatation of venules. There was a striking reduction in the inflammatory response during cortisone treatment. Four days after cortisone was stopped the tissue became intensely inflamed again and two days later had retracted off the central table.

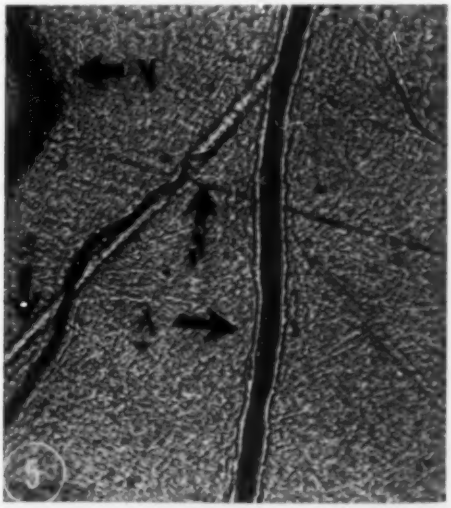


FIG. 5. An arteriole (A), two precapillaries (P) and venule (V) in an apparently normal chamber. A scratch on the cover-slip (S) runs diagonally across the field.

Effect of Cortisone on Apparently Normal Connective Tissue: Three animals were studied to determine the effects of the hormone on apparently normal chambers. Two of these animals had two chambers each, so that observations were made on a total of five chambers. The three animals received 5 mg. of cortisone for six, nine and 10 days, respectively. In two animals (three chambers), there was a significant increase in arteriolar tone after six days of cortisone (figures 5 and 6). In the third animal (two chambers), there was only a very slight increase in tone.

Tuberculous Infection: It is possible to inoculate living virulent tubercle bacilli directly into the thin layer of tissue on the observation table. In the unsensitized animal the initial response to the presence of living virulent bacilli is minimal.[12] With the development of hypersensitivity, however,

as evidenced by a positive tuberculin test, there is progressive vascular damage characterized by dilatation of blood vessels, sticking of white blood cells to endothelium, and diapedesis of cells through vessel walls. This is followed by hemoconcentration, stasis and thrombosis of small vessels, with infarction of tissue and subsequent liquefaction of the necrotic area. If a previously sensitized animal is used the explosive reaction begins immediately.

The effects of cortisone on tuberculous infection as observed in vivo have been reported [13] and are best summarized in terms of the usual pathologic change observed in vivo.

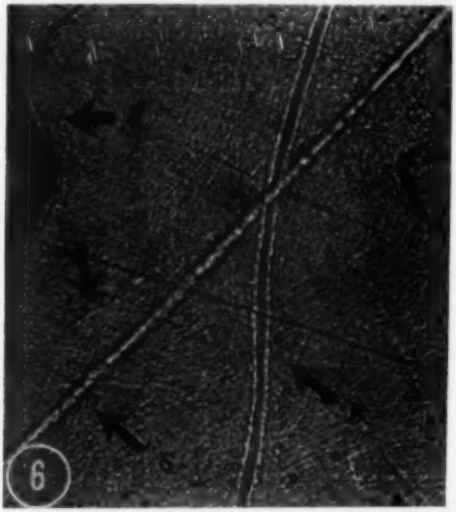


FIG. 6. The same arteriolar segment (A) seen in figure 5 after six days of cortisone therapy (10 mg./daily). There has been an increase in tone of the arteriole, and the precapillaries are not visible due to constriction of the precapillary sphincters. A portion of one of the precapillaries (P) can be seen adjacent to the scratch (S). It contains only plasma and is therefore difficult to visualize.

1. The usual vascular dilatation which accompanies reinfection tuberculosis is reduced during cortisone therapy.

2. The hormone causes a quantitative reduction in the damage to vascular endothelium, which characterizes reinfection tuberculosis. Hemoconcentration stasis and thrombosis of vessels still occur along the caseous margin of the tubercle, and there continues to be progression of the disease, but the vessels a short distance from the caseous edge appear more normal and the endothelium of these vessels tends to preserve its normal refractile appearance.

3. There is a reduction in the amount of exudate in the cortisone treated animal. This is probably related to the preservation of a more normal vascular endothelium, so that fewer cells migrate out of vessels.

It should be stressed that, in spite of the reduction in the over-all inflammatory response, there is continued extension of the caseous lesion. It is quite likely that the decrease in inflammation enables further multiplication of tubercle bacilli and facilitates their spread, so that the net result is further tissue damage.

Focal Reaction: If a dilute solution of old tuberculin is injected intravenously into an animal with a preëxisting tuberculous infection in the ear chamber, there will be an acute flare-up of the infection reaching a peak in from four to eight hours and persisting for from 24 to 48 hours. The reaction is dependent upon the state of hypersensitivity of the animal and provides a convenient measure for the in vivo study of allergy in tuberculous infection.

In the untreated animal the focal reaction is associated with the following changes: (1) increased sticking of leukocytes to vascular endothelium; (2) lability of the circulation, with periods of constriction alternating with marked dilatation and sluggish flow; (3) increase in exudate and free fluid; (4) hemoconcentration, stasis and thrombosis of vessels; (5) increase in the fluidity of the caseous area, and (6) hemorrhage. If each of these reactions is graded 1 plus to 4 plus, and the changes are added for any given experiment, a rough quantitative index of the extent of the focal reaction can be obtained. The maximal index would be 6 (types of pathologic change) $\times 4$ (maximal reaction) $= 24$. An index of 24 actually corresponds to complete destruction of the tissue on the observation table.

There is always some variation between different animals in the magnitude of the focal reaction, and to control this the focal reaction was studied in the same animal with and without cortisone treatment. The results of these studies on five animals are shown in table 1. In all but one (animal 114) the same tuberculous lesion was observed with and without cortisone therapy. The table shows the dates of the reactions, the amount of old tuberculin given intravenously and the dosage of cortisone. In animal 114 the right ear was infected first and cortisone treatment was given for the first 14 days after inoculation. (This animal had previously been sensitized with BCG.) The focal reaction was then induced and an index of 1.0 was obtained. At a later date, after cortisone therapy had been stopped, the left ear was infected and 14 days after inoculation the focal reaction was again observed. Without cortisone therapy the index was 10.

It will be seen in table 1 that the focal reaction was always less with cortisone therapy than without except in rabbit 93. This animal had been receiving streptomycin to control the extent of infection, and by the time the second and third focal reactions were observed (on June 20, 1950, and July 13, 1950), granulation tissue had extended into the caseous area and

the tubercle was largely healed. This may account for the similarity of results with and without treatment. In spite of this exception, the average index for all focal reactions during treatment (4.5) was considerably less than the average (14) without treatment.

Serum Sickness: Rich and Gregory [14] have described cardiovascular lesions in rabbits following large intravenous injections of horse serum which resemble those of rheumatic fever and periarteritis nodosa in man. Using the rabbit ear chamber technic Ebert and Wissler [11] demonstrated certain consistent vascular reactions following large intravenous injections of nor-

TABLE I

Focal Reaction With and Without Cortisone Treatment

Animal	Date	Dosage of Old Tuberculin	Focal Reaction with Cortisone Treatment		Index of Focal Reaction Without Treatment
			Dosage of Cortisone	Index of Reaction	
No. 93	4–27–50	3 c.c. 1:10 OT	10 mg./day 23 days	16.0	
	6–20–50	3 c.c. 1:10 OT	—		10.0
	7–13–50	3 c.c. 1:10 OT	—		16.0
No. 95	6–9–50	3 c.c. 1:100 OT	25 mg./day 5 days	2.0	
	6–20–50	3 c.c. 1:100 OT	—		11.0
	7–5–50	3 c.c. 1:100 OT	25 mg./day 4 days	0	
	7–19–50	3 c.c. 1:100 OT	—		13.0
No. 113	7–11–50	3 c.c. 1:100 OT	25 mg./day 7 days	4.5	
	7–25–50	3 c.c. 1:100 OT	—		15.0
No. 114 (right ear)	8–9–50	3 c.c. 1:100 OT	25 mg./day 14 days	1.0	
No. 114 (left ear)	10–30–50	3 c.c. 1:100 OT	—		10.0
No. 134	3–6–51	3 c.c. 1:100 OT	5 mg./day 29 days	3.6	
	3–19–51	3 c.c. 1:100 OT	—		24.0
Average index of reaction				4.5	14.0

mal horse serum (10 ml./Kg.) 18 to 20 days apart. Four to seven days after the first injection, localized constrictions and dilatations were seen in the walls of arterioles 30 to 60μ in diameter, and there was segmental sticking of leukocytes to arteriolar endothelium. These changes were greatly intensified after the second injection. Swelling of arteriolar endothelium was often seen after the second injection. Smaller arterioles showed minimal changes. Focal swelling and proliferation of venule endothelium were seen after the second injection. Minimal venule sticking and dilatation occurred simultaneously with arteriolar changes. Minimal sludging of

blood frequently developed four to seven days after the first injection, always becoming intensified immediately after the second, usually with a subsequent increase two to six days later. Platelet and white blood cell thrombi and emboli were seen during and immediately after the second injection. They were numerous for several hours but were rarely seen after 12 hours.

If a third injection of horse serum was given 18 to 20 days after the second, a reëxacerbation of the vascular reactions occurred similar to that seen after the second injection.

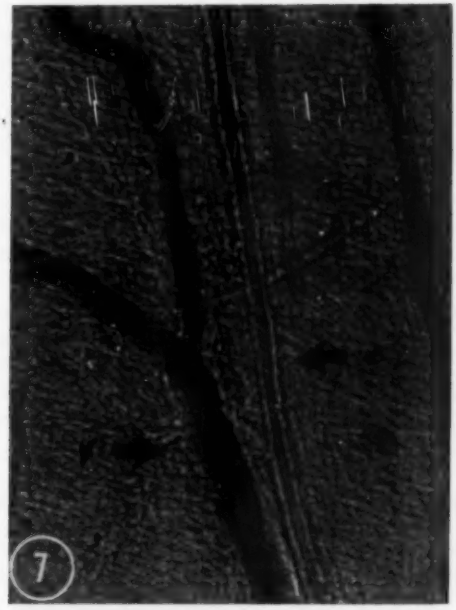


FIG. 7. Appearance of an arteriole (A) and adjacent venules 23 hours after the second injection of horse serum in an animal treated with cortisone (5 mg. daily for 18 days). The vessels appear normal.

Cortisone produced a quantitative reduction in the in vivo manifestations of serum sickness in rabbits as observed by the rabbit ear chamber technic.[18] Vascular tone was better maintained, vascular endothelium tended to keep its normal refractile appearance, swelling of endothelium was suppressed, and there was reduction in the sticking of leukocytes to endothelium. Sludging of erythrocytes was less marked, and platelet and white blood cell thrombi and emboli were less numerous in treated animals, but the suppression of these intravascular changes was less dramatic than the reduction of vascular damage. As a result of the increased integrity of vascular endothelium

there were a decrease in diapedesis of leukocytes and a reduction in the accumulation of exudate. The effects of cortisone were reversible, and after treatment was stopped an exacerbation of the vascular changes was observed.

Figures 7 and 8 demonstrate the effects of cortisone on vascular tone in serum sickness. In this experiment the animal was treated with 5 mg. of cortisone daily from the time of the first intravenous injection of horse serum. Figure 7 shows an arteriole 23 hours after the second injection of horse serum. (The second injection of horse serum was given 18 days after the first.) The tone is well preserved. Cortisone treatment was

FIG. 8. The same arteriolar segment (A) seen in figure 7, 23 hours after a third injection of horse serum. The animal had received no cortisone for 14 days. Note the dilatation.

stopped four days after the second injection of horse serum, and a third injection was given 14 days later. Figure 8 shows the same arteriole seen in figure 7, 23 hours after the third injection of horse serum. Note the degree of dilatation (figure 8) in the absence of cortisone, as compared with the normal vascular tone during treatment (figure 7).

DISCUSSION AND CONCLUSIONS

In all of the inflammatory reactions studied, whether specific or nonspecific, cortisone appeared to exert much the same effect. First, vascular

tone was better maintained. Even in the apparently normal chamber there was often a gradual increase in arteriolar tone. The change in tone in all inflammatory reactions was reversible, and vessels dilated again after cortisone was stopped. Second, there was a reduction in damage to both arteriolar and venule endothelium regardless of the type of inflammatory stimulus. Third, as a result of the increased integrity of vascular endothelium, there were a decrease in diapedesis of leukocytes and a reduction in exudate.

Although it could be argued that part of the effect on tuberculous infection, the focal reaction and serum sickness was due to reduction in antibody formation, the same argument would not hold for nonspecific inflammation.

The present studies do not reveal if this is a primary or secondary effect in vascular endothelium, but, regardless of the mechanism, this alteration in reactivity in the small blood vessels helps explain much of what is known of the clinical effects of cortisone. If the reactivity of small blood vessels is reduced, it becomes apparent that disease states will be favorably or unfavorably influenced according to the "usefulness" of the inflammatory response to the human organism. In an infection the vascular dilatation, increased permeability of blood vessels and diapedesis of leukocytes are useful in localizing and combating the infecting organism. In such a reaction cortisone should have a harmful effect, and this of course is true.[1, 2] If, on the other hand, it is possible to reduce the apparently useless inflammatory response in diseases such as rheumatoid arthritis, the patient will benefit.

BIBLIOGRAPHY

1. Mogabgab, W. J., and Thomas, L.: The effects of cortisone on bacterial infection, J. Lab. and Clin. Med. **39**: 271, 1952.
2. Spain, D. M., and Molomut, N.: Effects of cortisone on the development of tuberculous lesions in guinea pigs and their modification by streptomycin therapy, Am. Rev. Tuberc. **62**: 337, 1950.
3. Howes, E. L., Plotz, C. M., Blunt, J. W., and Ragan, C.: Retardation of wound healing by cortisone, Surgery **28**: 177, 1950.
4. Shwartzman, G., Schneierson, S. S., and Sofer, L. J.: Suppression of the phenomenon of local tissue reactivity by ACTH, cortisone and sodium salicylate, Proc. Soc. Exper. Biol. and Med. **75**: 175, 1950.
5. Jones, K. S., and Meyer, K.: Inhibition of vascularization of the rabbit cornea by local application of cortisone, Proc. Soc. Exper. Biol. and Med. **74**: 102, 1950.
6. Whitelow, N. J.: The treatment of severe burns with ACTH. Preliminary case reports, Proc. Second Clinical ACTH Conference **2**: 310, 1951.
7. Sandison, J. C.: Transparent chamber of rabbit's ear, giving complete description of improved technic of construction and introduction and general account of growth and behavior of living cells and tissues as seen with the microscope, Am. J. Anat. **41**: 447, 1928.
8. Ahern, J. J., Barclay, W. R., and Ebert, R. H.: Modification of the rabbit ear chamber technic, Science **110**: 665, 1949.

9. Clark, E. R., Hitchler, W. J., Kirby-Smith, H. T., Rex, R. O., and Smith, J. H.: General observations on the growth of new blood vessels into standardized chambers in the rabbit's ear and the subsequent changes in the newly grown vessels over a period of months, Anat. Rec. **50**: 129, 1931.
10. Cappell, D. F.: Intravitam and supravital staining, J. Path. and Bact. **32**: 595, 1929.
11. Ebert, R. H., and Wissler, R. W.: In vivo observations of the vascular reactions to large doses of horse serum using the rabbit ear chamber technique, J. Lab. and Clin. Med. **38**: 511, 1951.
12. Ebert, R. H., Ahern, J. J., and Bloch, R. G.: Development of tuberculous infection. In vivo observations in the rabbit ear chamber, Proc. Soc. Exper. Biol. and Med. **68**: 625, 1948.
13. Ebert, R. H.: In vivo observations on the effect of cortisone on experimental tuberculosis, using the rabbit ear chamber technique, Am. Rev. Tuberc. **65**: 64, 1952.
14. Rich, A. R., and Gregory, J. E.: The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity, Bull. Johns Hopkins Hosp. **72**: 65, 1943.
15. Ebert, R. H., and Wissler, R. W.: In vivo observations of the effects of cortisone on the vascular reaction to large doses of horse serum using the rabbit ear chamber technique, J. Lab. and Clin. Med. **38**: 497, 1951.

THYROIDITIS *

By George Crile, Jr., M.D., *Cleveland, Ohio*

The main reason for the progressive increase in the incidence of thyroiditis is better recognition. Nevertheless, the diagnosis of thyroiditis is still missed frequently or made late.

Since surgical intervention is rarely necessary in the treatment of thyroiditis, and since effective medical and radiologic treatment is available, it is extremely important that the diagnosis be made accurately and promptly so that needless operations can be avoided. This can best be done by bearing the possibility of thyroiditis in mind in connection with any enlargement of the thyroid and by confirming the diagnosis in questionable cases by biopsy of the thyroid with a Silverman needle.

Types of Thyroiditis

There are three separate and distinct types of thyroiditis: subacute or giant cell thyroiditis, struma lymphomatosa (Hashimoto's struma) and Riedel's struma. Riedel's struma is strictly a surgical problem and is so rare as to be of little clinical consequence. Unfortunately, many of the chronic varieties of subacute thyroiditis are called Riedel's struma by pathologists, and surgeons have often removed them believing that they were true Riedel struma. The disease described by Riedel is not removable because it involves not only the thyroid but also the entire cervical region, carotid sheath, trachea and muscles in such a way that the front of the neck is involved in a diffuse fibrosis which renders it absolutely impossible to do a thyroidectomy in the conventional sense of the word. These patients are invariably thought to have an inoperable cancer of the thyroid prior to biopsy, and the only reason for operation is to decompress the trachea.

Clinical Types of Subacute Thyroiditis

The most common type of thyroiditis is the subacute variety, which may manifest itself in a number of different ways. In its most severe fulminating form, the onset is quite sudden and is associated with severe pain in the thyroid, a high temperature and a marked systemic reaction. Frequently the patients are prostrated by their illness and the tachycardia is apt to be out of proportion to the fever. More often than not the patient comes to the physician complaining of a sore throat. The physician may look down the throat and examine the lateral cervical region but miss the tender enlargement of the thyroid which invariably accompanies this form of subacute thyroiditis. Antibiotics may be given on the assumption that the patient

* Presented at the thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 25, 1952.

has a pharyngitis, and it may be several days before the patient, whose symptoms are not relieved by antibiotic therapy, states that this sore throat is different from any he has had before, and the physician at last discovers the tender enlargement of the thyroid. During the acute phase of the disease, pain may be referred to the ear or to the jaw, and otolaryngologists or dentists may be consulted. We have seen patients who have been treated for ear infections and who have had teeth extracted at the onset of attacks of thyroiditis.

It is not uncommon for patients to have what they describe as a sore throat at the onset of the disease but to have a persistence of systemic symptoms after the subsidence of the local tenderness in the thyroid. A daily elevation of temperature may occur in these cases, and such patients may present the problem of a fever of unknown origin. Innumerable agglutination tests may be made, but no cause is found for the fever until the characteristic hard enlargement of the thyroid gland is palpated.

In some cases, after the subsidence of the acute symptoms the patients feel weak and nervous. They may lose weight, and sometimes tachycardia is present suggesting hyperthyroidism. In fact, in some cases the basal metabolic rate is elevated during the course of subacute thyroiditis, and a diagnosis of hyperthyroidism may be made and thyroidectomy advised. In other cases, the symptoms resemble those of chronic nervous exhaustion and may be interpreted as being due to functional causes or to the menopause. In cases in which local symptoms persist in the thyroid area after subsidence of the pain, the choking sensation and feeling of pressure of which the patient complains may be interpreted as globus hystericus. In other cases the persistent hard enlargement of the thyroid may arouse the suspicion of malignancy, and in cases in which only one lobe is involved a diagnosis of adenoma of the thyroid may be made.

Diagnosis of Subacute Thyroiditis

In subacute thyroiditis, the thyroid gland is not often enlarged to more than twice its normal size, but it has a characteristic hard consistency and more often than not is moderately tender. If there is a history of pain in the region of the thyroid, and a diffuse, hard, slightly tender enlargement of the entire thyroid gland is present, there is no difficulty in making a diagnosis of subacute thyroiditis. If, however, only one lobe is involved, or if one lobe is much larger than the other, and particularly if the gland is not tender, it is impossible to rule out malignancy. It is in these cases that biopsy with the Silverman needle is of the greatest value. We have performed needle biopsies of the thyroid in over 200 cases without encountering any complications, and the procedure can be done in the office and leaves no visible scar.

Almost all patients with subacute thyroiditis, even when it has entered the chronic stage and is no longer tender, have striking elevations of the

sedimentation rate and extremely low uptakes of radioactive iodine. Even when the basal metabolism is elevated and there are clinical signs and symptoms of hyperthyroidism, the uptake of radioactive iodine is apt to be nil. This finding can best be explained by the hypothesis that preformed colloid is being absorbed and that the hyperthyroidism is an artificial or induced hyperthyroidism similar to that which takes placce when desiccated thyroid is administered.

Although thyroiditis may be localized to one area in the thyroid, it usually involves all of one lobe and spreads gradually to involve the entire gland. Sometimes it has subsided completely in one lobe by the time the other is involved. The most helpful diagnostic feature of subacute thyroiditis is the fact that usually the entire lobe is diffusely involved so that it retains its shape, thus differing from a lobe involved by an adenoma or a carcinoma except in the rare cases of carcinoma which infiltrates the entire thyroid diffusely. It is because of the possibility of carcinoma that nontender and slightly tender thyroids should be subjected to needle biopsy.

Etiology of Subacute Thyroiditis

The cause of subacute thyroiditis is not known, but it is possible that it represents a virus infection in which there is damage to the cells lining the follicles. Colloid escapes into the tissue spaces and there provokes a foreign body reaction and attracts wandering cells which phagocytize the colloid.

Treatment

Although subacute thyroiditis is a self limited disease which ultimately subsides without causing permanent damage to the thyroid, it may persist and cause symptoms for a year or more if treatment is not instituted. X-ray therapy in doses of 600 to 800 r usually will cause a prompt and complete subsidence of all symptoms and signs of subacute thyroiditis. Oftentimes the patient is free of pain within 24 hours of the time of the first x-ray treatment, and usually within three weeks the thyroid has returned nearly to normal and at the end of six weeks is no longer palpable. Sometimes recurrence of symptoms or spread to the other lobe requires a second course of therapy. It is said that administration of thiouracil will accomplish similar results and hasten the natural resolution of the inflammatory reaction.[1] Propylthiouracil is not effective. We have not seen hypothyroidism or any other complications following subacute thyroiditis, nor has suppuration occurred in any of the cases we have treated. Antibiotics appear to be of no value.

ACTH or cortisone affords immediate relief of the symptoms followed in two or three days by striking reduction in the size of the thyroid, abolition of tenderness, and softening of the gland, but all signs and symptoms recur promptly after short courses of treatment.

Struma Lymphomatosa

Struma lymphomatosa may be even more common than subacute thyroiditis, but since it does not cause severe symptoms patients do not frequently consult physicians for treatment. In the past we have recognized struma lymphomatosa in its surgical form and have not realized how commonly milder forms of the disease are found if looked for.

Histologically, struma lymphomatosa is characterized by oxyphilic changes of the thyroid epithelium, fibrosis, infiltration of lymphocytes and the presence of germinal lymph follicles. Clinically, the irregular lobulations of the thyroid and the tendency to asymmetry usually result in a clinical diagnosis of nodular goiter, and thyroidectomy is often recommended to relieve the symptoms of pressure and vague discomfort in the neck. Myxedema commonly follows thyroidectomy performed for struma lymphomatosa. Since the enlargement of the thyroid usually can be controlled either by administration of large doses of desiccated thyroid or by x-ray therapy given in doses up to about 1800 r, there is rarely any indication for thyroidectomy.

Diagnosis of Struma Lymphomatosa

The frequency with which struma lymphomatosa will be recognized depends largely upon awareness of the frequency of this condition and upon considering it in the differential diagnosis of any nodular goiter which involves both lobes of the thyroid. Struma lymphomatosa is, moreover, usually associated with a tendency to hypothyroidism, or at least with a basal metabolic rate of less than 0 per cent, and this fact differentiates it from nodular goiter, which usually is associated with basal metabolic rates above zero and rarely is associated with hypothyroidism. The entire thyroid is diffusely involved in almost all cases of struma lymphomatosa, but the irregular bosselations and the tendency for one lobe to be larger than another frequently make the goiter feel very nodular. Its firm, rubbery consistency, however, is quite characteristic and is harder than the average nodular goiter. If all suspiciously firm goiters which involve both lobes of the thyroid more or less diffusely are subjected to needle biopsy, a number of cases of struma lymphomatosa or lymphoid thyroiditis will be found and many unnecessary operations can be avoided.

Lymphoid Thyroiditis

Lymphoid thyroiditis may be an early phase of struma lymphomatosa or it may be an entirely different entity. It shows the same lymphocytic infiltration and the presence of germinal follicles as does struma lymphomatosa, but fibrosis is minimal or absent and the oxyphilic epithelium is not seen. These patients, like those with struma lymphomatosa, tend to have low basal metabolic rates and clinical evidence of mild hypothyroidism. The

disease occurs predominantly in females, is common in the age group from 20 to 40, and frequently develops following childbirth. The only symptom is a progressive diffuse enlargement of the thyroid, which may become three or four times its normal size, may cause mild pressure symptoms or feelings of discomfort, and may become quite conspicuous.

Treatment of Lymphoid Thyroiditis

Lymphoid thyroiditis responds promptly and dramatically to treatment with large doses of desiccated thyroid. If 3 gr. of U.S.P. thyroid are given daily the enlargement of the thyroid usually disappears within a period of two or three months, and the thyroid loses its firm consistency and oftentimes is not palpable at all three months after the onset of therapy. The cause of lymphoid thyroiditis and struma lymphomatosa is unknown, but since they are benefited so strikingly by the administration of large doses of desiccated thyroid it is possible that they represent an exhaustion response of the thyroid, and that the changes are reversible by putting the thyroid entirely at rest. This treatment is much more physiologic than thyroidectomy, and many needless operations can be saved if the physician will bear in mind the possibility of lymphoid thyroiditis in all cases of enlarging diffuse goiters, and will consider struma lymphomatosa in all cases in which there is a firm nodular enlargement of the entire thyroid. When the diagnosis has been confirmed by needle biopsy, medical treatment with desiccated thyroid will cause prompt resolution of the goiter in all cases of lymphoid thyroiditis and in some cases of struma lymphomatosa. X-ray therapy may also be of some value in diminishing the size of the goiter. In one case of struma lymphomatosa cortisone caused a striking decrease in the size of the goiter, but it recurred promptly when treatment was discontinued.

Summary

1. The three main types of thyroiditis are subacute or giant cell thyroiditis, struma lymphomatosa (Hashimoto's struma) and Riedel's struma.

2. Riedel's struma is very rare, simulates inoperable cancer, and often requires surgical decompression of the trachea.

3. Subacute thyroiditis varies in its clinical manifestations from a very acute disease accompanied by pain, tenderness, fever and prostration, to a very chronic process which may simulate adenoma or carcinoma of the thyroid, globus hystericus or fever of unknown origin.

4. In questionable cases of subacute thyroiditis, the diagnosis should be confirmed by biopsy with the Silverman needle.

5. X-ray therapy causes prompt and usually permanent remission of the symptoms and signs of subacute thyroiditis. Cortisone or ACTH causes immediate remissions but recurrence takes place promptly after short courses of treatment.

6. Struma lymphomatosa simulates nontoxic nodular goiter and is rarely recognized unless it is borne in mind in all patients with firm bilateral nodular goiters. If the basal metabolism is below zero or clinical hypothyroidism is present, the probability of struma lymphomatosa is increased.

7. The diagnosis of struma lymphomatosa can be confirmed by biopsy with the Silverman needle.

8. Lymphoid thyroiditis occurs commonly in women 20 to 40 years of age and causes a smooth, firm, symmetrical enlargement of the thyroid simulating a diffuse colloid goiter.

9. Both lymphoid thyroiditis and some cases of struma lymphomatosa respond specifically to treatment with desiccated thyroid in doses of 3 gr. daily. X-ray therapy also may be of value. Cortisone or ACTH may cause transitory remissions.

BIBLIOGRAPHY

1. King, B. T., and Rosellini, L. J.: Treatment of acute thyroiditis with thiouracil, J. A. M. A. 129: 267-268 (Sept. 22) 1945.

THE APPLICATION OF CYTOLOGIC DIAGNOSIS TO CANCERS OF THE STOMACH, PANCREAS AND BILIARY SYSTEM *

By HENRY M. LEMON, M.D., *Boston, Massachusetts*

CARCINOMAS of the stomach, biliary tract and pancreas constitute one of the principal causes of death from cancers in both males and females. Not only are these malignant growths among the most frequent of all types of cancer, but they are also among those with the highest mortality rate in spite of therapy. Diagnosis of these tumors remains highly unsatisfactory, partly because their natural history is such that symptoms necessitating medical attention develop late, and partly as a result of the inaccessibility of some of the growths to radiologic or endoscopic methods of visualization.

These diagnostic difficulties have perennially faced physicians. Within a year of the first successful surgical extirpation of cancer of the upper gastrointestinal tract by Billroth in 1881, Rosenbach published some of the first observations of tumor particles in gastric contents, as a diagnostic aid in gastric cancer.[1] Between this time and the introduction of the roentgen-ray into clinical diagnosis 20 years later, considerable work was carried out, indicating the possibilities of cytologic diagnosis of gastric cancer, utilizing both fresh and stained preparations and a variety of technics including gastric curettage. This type of approach was extended to the biliary tract about 30 years ago by the work of Lyon, who was impressed by the frequency with which normal columnar epithelium was desquamated into bile in inflammatory disease of the gall-bladder.[2]

Recently, renewed interest has developed in cytologic diagnosis of cancer, in the hope that earlier detection may be possible. In nearly all types of cancer, improvement in the end results of surgical therapy rests with the internist rather than with the surgeon, who can extend but slightly farther the radical scope of his procedure.

During the past five years in our clinic we have investigated the application of cytologic methods to diagnosis of tumors arising in the gastrointestinal tract and its accessory glandular structures. We have utilized the fixing and staining procedures developed by Dr. G. N. Papanicolaou which have been so successful in improving detection of uterine and bronchogenic carcinomas.[3] The procedure can be readily mastered by house officers or technicians and provides excellent preservation of the details of nuclear and

* Presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 24, 1952.

From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals and the Department of Medicine, Boston University School of Medicine.

The studies were carried out with partial assistance of cancer teaching grants from the National Cancer Institute, National Institutes of Health, Federal Security Agency.

cytoplasmic structure of clusters of cells, upon which the diagnosis depends. For broadest possible clinical application, we have obtained our secretions using Levin or Rehfuss tubes, collecting both the fasting contents and the results of a brief saline lavage. Sodium chloride solution in physiologic concentrations is utilized for gastric lavage, and 33 per cent magnesium sulfate for duodenal drainages.

There are three conditions which must be fulfilled for successful results: First and foremost, there must be meticulous preparation of the patient prior to examination. The upper gastrointestinal tract must be empty, in a resting secretory state, and not involved by chronic unrelieved obstruction or excessive inflammation. All obstructed cases should have 12 to 24 hour continuous aspiration prior to examination. After all, exfoliative cytologic diagnosis depends upon trapping and identifying healthy living cells from epithelial surfaces. Second, the physician must himself supervise every step in the procurement of gastroenteric contents and their handling until the time that the smears are wet-fixed. Chilling in an ice bath during collection and speed of handling will minimize proteolytic cell destruction, while neutralization of acid secretions will partly dissolve mucus, permitting adequate cell concentration by centrifugation at 1,800 revolutions per minute for 10 minutes.

Third, accuracy of interpretation depends upon adequate training of the individual, whether internist, pathologist or technician, in the recognition of cell types emanating from the particular region of the gastrointestinal tract examined. This experience can be obtained in a number of special centers now carrying on research in cytodiagnosis and is within the reach of most gastroenterologists, who will correlate clinical and cytologic findings over a period of several years.

Much less important are the details of technic, which are still under experimental development. It is quite likely that some type of gastric curettage by an abrasive balloon, similar to that introduced recently by Panico, Papanicolaou and Cooper, will increase the number of neoplastic cells recovered in gastric contents.[4] Enzymatic treatment of the aspirate with papain may also aid in concentration of the specimen, but these additions to the procedure all definitely increase the complexity and time required, thus hindering clinical application of the method.[5]

What can be expected of the method when it is applied to the common gastric problems of medical practice, including many normal individuals with functional problems, atrophic and hypertrophic gastritis, benign gastric ulcer, achlorhydria and gastric cancer? The results of our series of gastric aspirations for tumor cells are shown in table 1. In 12.8 per cent of the cases we were unable to repeat the examination until a satisfactory smear free of retention or digestion was obtained, and in 11.3 per cent of cases false-positive or false-negative smears were obtained. In the remaining three quarters of the entire series the results of the gastric smear corre-

sponded well to the pathologic lesions demonstrated in the patients by tissue section, laparotomy, x-ray, gastroscopy or clinical follow-up for a year or more. It is apparent that the major difficulty is the rarity of recognizable neoplastic cells in the gastric contents of many patients with proved and extensive gastric carcinoma, resulting in 50 per cent false-negative results despite our best efforts. False-positive cases, in our experience, were most often associated with gastritis (by pathologic diagnosis), in which there appears to be an unusually extensive exfoliation of somewhat abnormal cell types. Nearly all of our cancer cases were hospitalized patients with far advanced disease, from whose ulcerated necrotic tumors we could expect a minimal exfoliation of viable well preserved tumor cells. One intraepithelial carcinoma with an ulcerated area less than 1 mm. across was missed cytologically, but excellent positive smears were obtained from several gastric ulcers of benign gross appearance. One wholly unsuspected case of far

TABLE I

Cytodiagnosis of Gastric Carcinoma

Total Cases:	273	
Cancer patients	17.2%	42 cases
Diagnosis verified by laparotomy or pathology	40.3%	100%
Report of Smear:		
Unsatisfactory	12.8%	7.1%
Negative, correct	64.5%	
Negative, false	9.5%	50.0%
Questionable	5.9%	14.3%
Positive, correct	5.5%	28.6%
Positive, false	1.8%	
	100.0%	100.0%

advanced gastric cancer was turned up in a control patient thought by x-ray to have an obstructing duodenal ulcer.

Our results are quite similar to those obtained by Seyboldt, Papanicolaou and Cooper in a much larger series of cancer patients.[6] Furthermore, a review of the literature since 1882, covering 556 cancer patients in a total of 2,375 patients whose gastric contents were examined, indicates essentially the same accuracy for this method of diagnosis.[7] Again, 5.5 per cent of reported smears were unsatisfactory, and 14.0 per cent of smears were falsely negative or positive in the entire series, with an over-all accuracy in the vicinity of 79.5 per cent. Again, nearly half of all gastric carcinomas went undetected. On the basis of the collected experience, it would be fair to conclude that cytologic diagnosis of gastric neoplasms may be of assistance in determining the etiology of gastrointestinal symptoms where other diagnostic methods have yielded inconclusive results. Delay in the recognition of the malignant origin of grossly benign gastric ulcers may be avoided by careful and repeated study of the gastric sediment for tumor cells, such as those seen in figure 1, obtained from case 1.

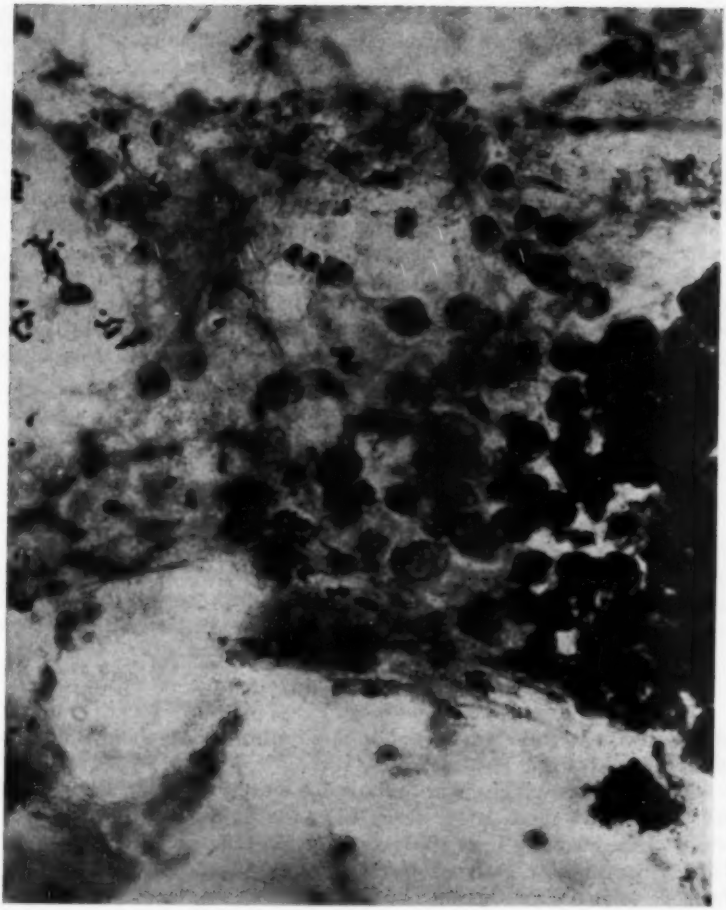


FIG. 1. Group of gastric carcinoma cells found in gastric contents from case 1. Note the excessively large ratio of nuclear to cytoplasmic volume, and the tendency for small cell groups to break away from each other, unlike normal columnar epithelium. (× 800).

CASE REPORTS

Case 1. A 62 year old male had suffered from nocturnal epigastric distress for three years, relieved by food and alkalies. Initially, fluoroscopic examination of the upper gastrointestinal tract with barium revealed no abnormality in the stomach or duodenum. His symptoms were controlled for three years by an ulcer diet, but recurred with vomiting three weeks before admission. At this time roentgen examination revealed a gastric ulcer with a suspiciously rigid margin. There had been

no symptoms such as weight loss. Physical examination revealed a lean, well preserved male without signs of disease. There was no anemia and no occult blood in his stool. The gastric acidity reached 17 clinical units after histamine, 39 clinical units after insulin, and 15 clinical units during night secretion. Many clumps of tumor cells were noted in the gastric contents. A superficial gastric ulcer 3 cm. in diameter was removed in September, 1946, by subtotal gastric resection, which the surgeon and pathologist could not say was malignant by gross appearance. Undifferentiated adenocarcinoma was found in the margin and base of the ulcer, but the regional nodes were not involved. The patient did well, gaining eight pounds during the first year after treatment, but died in March, 1950, as a result of metastases to the pituitary and adrenal glands.

The method may also assist in the investigation of melena of undetermined origin and in the follow-up of patients with achlorhydria or pernicious anemia, but it is not suited for the screening of large numbers of clinic patients as is the vaginal smear technic.

Because of the many false-negatives, only repeated negative examinations are significant. Since the method is not suited for screening of patients because of the time and care necessary for preparation of patients and search for tumor cells, it is of little practical utility in aiding the earlier recognition of gastric cancers, which perforce must be symptomatic and reasonably well advanced before opportunity for cytodiagnosis occurs. In many cases, roentgen-ray or gastroscopic examination will already have suggested the possibility of tumor and determined the proper course of action.

These considerations prompted us to apply the cytologic method to investigation of duodenal contents for tumor cells in patients with carcinoma of the pancreas, biliary tract and liver.[8] Alternative diagnostic methods are by no means so conclusive for these tumors, which have been favorite topics for clinicopathologic conferences for many years.

Furthermore, in a minority of cases pain or obstruction of the common bile duct provides an early sign of cancer necessitating medical care. It was thought that an improvement in the methods used for distinguishing the etiology of obstructive jaundice would result in lessening the delay prior to operation which has been the rule heretofore for patients with carcinomatous involvement of the biliary tract or pancreas.

The position of the tip of the tube requires somewhat more careful placement for duodenal drainage than for gastric aspiration, particularly in icteric patients where the secretion is not obviously bile tinged. Also, the soaplike activity of bile salts necessitates more care in preparation of the smears, using chemically cleaned slides, tubes free of oil or grease, and the addition of a celloidin jacket about the smears prior to staining. Otherwise, the method is but an extension of that used in gastric cytodiagnosis.

The results of observations of the first 105 patients whose disease has been pathologically or surgically verified are presented in table 2. Only 9 per cent of those cases had unsatisfactory smears, which were not repeated with satisfactory results. Nearly two thirds of 37 primary cancers of the

liver, gall-bladder, bile ducts and pancreas had recognizable malignant tumor cells in duodenal contents. Fourteen per cent of all cases were erroneously interpreted. The significance of positive smears was increased by the infrequency with which tumor cells from metastatic carcinomas invading the liver were exfoliated into the bile. Several primary tumors less than 2.0 cm. in diameter exfoliated abnormal cell types which were readily recognized in the drainages. In all except four or five cases of primary carcinoma the diagnosis was suspected on the basis of the preoperative or antemortem examination of the smear without knowledge of the clinical condition of the patient.

Of considerable importance is the fact that nine out of 12 patients with positive or questionable drainages in pancreatic cancer had obstructive jaundice with acholic stools, which was also the case with half of the patients with negative drainages. In five of these 12 pancreatic cancer patients with

TABLE II

Cytodiagnosis of Hepatic, Biliary Tract and Pancreatic Carcinoma

Total Cases	105	Primary Carcinoma	Metastatic Carcinoma
Cancer cases	47%	37 cases	12 cases
Diagnosis verified by laparotomy or pathology	89%	97%	100%
Report of Smear:			
Unsatisfactory	9%	5%	8%
Negative, correct	50%		
Negative, false	13%	33%	67%
Questionable	13%	27%	17%
Positive, correct	14%	35%	8%
Positive, false	1%		
	*100%	100%	100%

* Metastatic carcinomas excluded in calculation of these over-all percentages.

positive drainages, roentgen examination of the duodenal loop showed no widening or disturbance of the mucosal pattern. In carcinomas of the gall-bladder and upper biliary tract with positive smears, roentgen manifestations of the disease were seldom found, although striking physical signs of a tumor mass in the right upper quadrant were frequent.

Case 2. A 60 year old white male entered the hospital partially disoriented, with abdominal swelling of eight months' duration and jaundice of six months'. He had a long history of alcoholism and had had periumbilical intermittent pain, anorexia, constipation, chills, fever and a 40 pound weight loss with his illness. Both liver and spleen were markedly enlarged, stools were acholic with occasional occult blood, and x-ray revealed an irregular filling defect in the superior aspect of the first portion of the duodenum.

The first duodenal drainage was unsatisfactory because of excessive hematin; when repeated, it showed red cells and many clumps of typical tumor cells and normal cells (figure 2). Two liver punch biopsies were unsuccessful and were followed by ascites. The ascitic fluid did not contain tumor cells. At autopsy a papillary adeno-

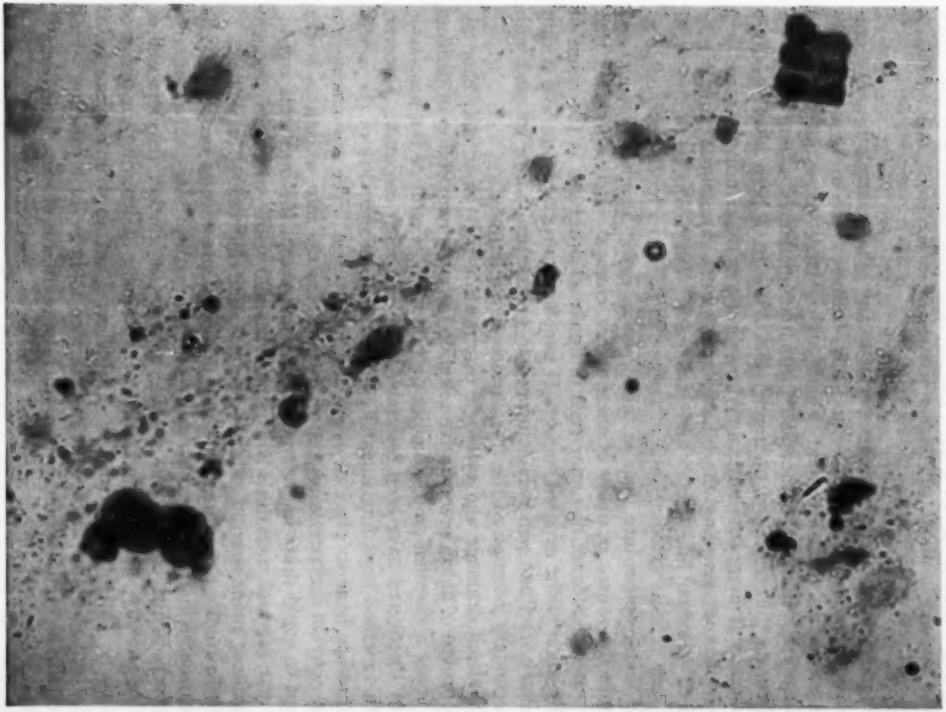


FIG. 2. Exfoliated cancer cells from papillary adenocarcinoma of ampulla of Vater, found in duodenal drainage from case 2 (lower left). Note contrast with exfoliated normal columnar epithelium in same field (upper right), upon which accurate cytologic diagnosis of cancer may be made. (×800).

carcinoma of the ampulla of Vater was found which measured 1.5 cm. in diameter and which had not metastasized either locally in the pancreas or to regional nodes or distant organs. This tumor encircled the exit of the common bile duct and contained a 3 mm. shallow surface ulcer. The patient also had extensive diffuse biliary cirrhosis, perforation of the gall-bladder with localized peritonitis, and thrombosis of the portal vein as the cause of the ascites.

Duodenal contents have been superior to any other gastrointestinal secretion in our experience for cytologic study, because there are few cells normally present in this secretion. Furthermore, large quantities of normal columnar epithelium are desquamated in pathologic states, aiding greatly in the accurate differentiation of tumor cells. We have been able to obtain specimens containing both normal and neoplastic epithelium in the same field from hepatomas invading the biliary tract,[8] from carcinomas of the gall-bladder,[9] common bile duct [10] and pancreas.[9] The frequent profusion of these cells renders cytodiagnosis of tumors in this area more dependable as a case finding procedure than in the stomach, even though we cannot yet ascertain the source of many of these tumor clumps. It is our belief that the greater abundance of tumor cells in duodenal drainages is the result of less digestion of the exposed surfaces of neoplasms arising from deep within the biliary tract and pancreas compared to gastric neoplasms, coupled with less secondary infection of the free surface of the tumor.

Duodenal drainage and cytologic examination for tumor cells have already proved of aid in preoperative selection for early exploration of patients with upper abdominal pain, jaundice or tumors. Several of the neoplasms thereby discovered have been resectable.[10, 11] We must recognize, however, that this method rests fundamentally upon the peculiar ability of the cancer cell to escape from its place of origin and metastasize. We are making use of the *external* metastasis of gastrointestinal cancers into secretions in the attempt to avoid delay in treatment, and must accept the inevitable conclusion that *internal* metastasis via lymphatics and veins will be a frequent concomitant manifestation of disease often nullifying our efforts.

These studies demonstrate without doubt the presence of neoplastic cells in gastrointestinal secretions of many patients with primary carcinomas in the upper digestive tract and provide a basis for further development of accurate technic. Any method such as this capable of detecting the presence of cancer in patients with tumors as small as 2 cm. in diameter can be of great diagnostic and therapeutic significance to individual patients. This method can be of most clinical value where other means of recognizing cancer are least successful in practice, and it deserves further clinical trial with reference to the detection of pancreatic and bile duct carcinomas.

BIBLIOGRAPHY

1. Rosenbach, O.: Über die Anwesenheit von Geschwulst Partikeln in dem durch die Magenpumpe entleerten Magenhalte bei Carcinoma ventriculi, Deutsche med. Wchnschr. **8**: 452-453, 1882.

2. Lyon, B. B. V.: Non-surgical drainage of the gall tract, 1923, Lea and Febiger, Philadelphia.
3. Papanicolaou, G. N., and Traut, H. F.: Diagnosis of uterine cancer by the vaginal smear, 1943, Commonwealth Fund, New York.
4. Panico, F. G., Papanicolaou, G. N., and Cooper, W. A.: Abrasive balloon for exfoliation of gastric cancer cells, J. A. M. A. **143**: 1308, 1950.
5. Rosenthal, M., and Traut, H. F.: The mucolytic action of papain for cell concentration in the diagnosis of gastric cancer, Cancer **4**: 147–149, 1951.
6. Seyboldt, J. F., Papanicolaou, G. N., and Cooper, W. A.: Cytology in the diagnosis of gastric cancer, Cancer **4**: 285–295, 1951.
7. Byrnes, W. W., and Lemon, H. M.: Cytologic diagnosis of gastric carcinoma, in preparation.
8. Lemon, H. M., and Byrnes, W. W.: Cancer of the biliary tract and pancreas, diagnosis from cytology of duodenal aspiration, J. A. M. A. **141**: 254–257, 1949.
9. Lemon, H. M.: Early diagnosis of cancer, M. Clin. North America **34**: 1381–1408, 1950.
10. Lemon, H. M.: The clinical value of duodenal drainage in the diagnosis of carcinoma of the biliary tract and pancreas, New York State J. Med. **51**: 2155–2158, 1951.
11. McNeer, G., and Ewing, J. H.: Exfoliated pancreatic cancer cells in duodenal drainage: a case report, Cancer **2**: 643–645, 1949.

GASTRIC CANCER ON ULCER: A CLINICAL ANALYSIS OF A SERIES OF CASES CONFORMING PATHOLOGICALLY TO THE CRITERIA FOR MALIGNANT CHANGE IN PEPTIC ULCER OF THE STOMACH *

By THEO. R. WAUGH, M.D., and MORRIS D. CHARENDOFF, M.D.,
Montreal, Canada

THE incidence of the development of malignancy in a chronic peptic ulcer of the stomach has been a controversial subject among internists, surgeons and pathologists for many years. An extraordinary and in fact incredible difference of opinion is reported in the medical literature. Wilson and MacCarty in 1909 [14] stated that 71 per cent of apparently benign peptic ulcerations in this organ on careful microscopic examination showed carcinoma. Newcomb,[11] on the basis of strict criteria, found that 13 per cent of cancers showed evidence of an antecedent peptic ulcer, and that 3 to 7 per cent of peptic ulcers revealed malignant change. Ewing [6] was of the opinion that approximately 3 per cent became cancerous, and this figure is accepted by most pathologists. A lower incidence of 1 per cent was estimated by Borrmann,[2] who stressed the well known aphorism, "Cancers ulcerate, but ulcers do not carcinate," and in fact there are those who will not admit the possibility.

A new angle has been projected into this controversy by the more recent introduction of the concept of carcinoma in situ. This term, coined by Broders,[5] designates a neoplastic lesion having certain morphologic and, more particularly, cytologic features of carcinoma, but lacking evidence of spread and invasion beyond its local site. Attention had been directed to the presence of this type of lesion in the cervix by Schiller,[13] in the skin by Bowen [3] and in the endometrium by Hertig.[8] In 1940 Mallory [10] reported four cases of peptic ulcer of the stomach with carcinoma that he explained on the basis of a preëxisting, non-invasive stage of cancer which had undergone secondary, typically peptic ulceration. Such ulcers show malignancy only at the edges and hence, as he pointed out, might well have been wrongly considered cancer on ulcer. Moreover, as it is believed possible for carcinoma in situ to remain as such for many years, it may be some time before actual invasion takes place. On the basis of his findings he emphasized "the necessity for the greatest caution in attempting to interpret from the histologic picture, the genesis of a malignant ulcer."

* Received for publication March 17, 1952.
From the Department of Pathology, Division of Surgical Pathology, McGill University, Montreal. Case histories were made available through the courtesy of the Department of Surgery, Royal Victoria Hospital, and Dr. Harold S. Hooper, Grand'Mere, Quebec.

In 1949 a panel discussion on *The Relationship of Gastric Ulcer to Gastric Cancer* was presented at the Annual Scientific Session of the James Ewing Society, with George T. Pack [12] as Moderator. After a definition of terms, many aspects of the problem were discussed thoroughly, including clinical, pathologic and roentgenologic features. The following question was then put by the Moderator, "How many bona fide specimens have you personally seen—or patients treated—in which a benign gastric ulcer undoubtedly preceded gastric cancer?" The replies by the participants in the discussion were extraordinarily and predominantly negative. Such a response certainly indicated a distinct swing from the older accepted views.

As we have examined a number of stomachs over a period of years in which a pathologic report of carcinoma on ulcer was submitted to the surgeon, we felt it would be interesting to analyze the case histories. From the sections of tissues would be selected only those which conformed closely to rigid histopathologic criteria for this diagnosis. Then the histories of all of these cases would be examined and the findings included in the study. In this way the pathologic diagnosis would in no way be influenced by knowledge of the clinical history, signs or symptoms.

The following criteria were employed for the diagnosis of cancer on ulcer in the selection of our cases: the presence of a peptic ulcer of the stomach with carcinoma in the wall of the ulcer. The ulcer shows microscopic evidence of the typical four zones of exudation, necrosis, granulation and cicatrization described by Askanazy.[1] It has penetrated into or through the muscular coat of the organ. The surrounding and adjacent vessels exhibit evidence of an obliterating endarteritis, and the muscularis mucosae is fused with the muscular coat at the margin. The carcinoma is histologically of a type that could arise from the mucosa and has invaded the submucosa in the side wall of the ulcer but does not involve the base.

Over a period of approximately 20 years, 263 gastric resections were carried out in the Royal Victoria Hospital in which pathologic examination showed the presence of carcinoma. In 21 of these (or 8 per cent), the probability or possibility that the cancer had arisen on a peptic ulcer was mentioned in the report. These slides were reviewed and 10 were found to conform to the rigid criteria stated above. The clinical histories and findings in these 10 cases were studied and constitute the basis of this report.

Case Reports

Case 1. A 55 year old timber foreman was admitted with a history of epigastric pain following meals which was relieved by food and antacids. The complaints had persisted for three years, and frequently occurred during the night. Various diets had given only temporary relief. Gastric analysis showed no free acid. Roentgenographic examination showed a large ulcer crater on the lesser curvature which failed to respond to medical therapy. Two days prior to admission the patient vomited some coffee-ground material and passed dark stool. Surgical exploration was carried out to exclude a gastric carcinoma. The lesion was situated on the lesser

curvature and posterior surface 5 cm. from pylorus and measured 5.5 cm. in diameter. The edges were rolled and nodular and the base hard. This patient died one year postoperatively of metastatic carcinoma.

Case 2. A 41 year old Hungarian housewife was admitted in shock with a history of vomiting bright red blood, dizzy spells, weakness and a two year story of epigastric distress. She was treated by transfusion until her condition had improved sufficiently to warrant surgical intervention. A roentgenogram 18 months prior to admission had revealed a gastric ulcer. She was temporarily relieved by diet and stomach powders, but a subsequent roentgenogram failed to show signs of healing. More recently the pain had become boring in nature and was felt in her back. This patient's mother had died at 64 with a carcinoma of the stomach. In view of her family history, cancer was strongly suspected in this case. Pathologic studies verified this suspicion. The patient died of her disease two and one-half months postoperatively, with recurrence of growth. In this case, the lesion at operation was located on the posterior wall near the lesser curvature 1.5 cm. from the pylorus and measured 4 cm. in diameter. The edges of the ulcer were hard and rubbery. The regional lymph nodes were already involved.

Case 3. A 46 year old salesman entered hospital with a story of epigastric and substernal intermittent pain of three years' duration. The attacks occurred one to two hours after meals and were relieved by soda. He never followed a dietary regimen. Recently vomiting had accompanied the pain, occasionally with the presence of coffee-ground material. An ulcer crater was shown on the lesser curvature by roentgenograms. Gastric analysis showed free acid to be present. Surgical exploration revealed an ulcer on the lesser curvature, with some palpable enlarged regional lymph nodes. The ulcer was found on the lesser curvature 6 cm. from the pylorus and measured 2 cm. in diameter. There was considerable inflammatory reaction about it. This patient has survived for three and one-half years.

Case 4. A 65 year old merchant entered hospital with a history of gnawing sensations in the epigastrium for five years, accompanied by pressure and distention. He had received limited benefit from diet and medicines. Recently he had noted coffee-ground material in his vomitus, and he had passed tarry stools on several occasions. Gastric analysis revealed a high content of free acid. Roentgenographic studies showed a benign ulcer crater on the lesser curvature and posterior wall. At operation an ulcer was found penetrating into the pancreas, and a subtotal resection of the stomach was performed. The lesion was present in the middle of the lesser curvature and measured 2.5 cm. in diameter. The edges were rolled and the base was ragged and firm. This patient has survived for one and one-half years.

Case 5. A 65 year old pulp-mill worker complained on admission of digestive trouble which had extended over a period of "several years." More recently there had been vomiting. A gastric analysis was not done, and there was no history of hematemesis or tarry stools. The patient had seen a doctor for the first time shortly before admission. Roentgenographic examination showed a filling defect at the lower end of the stomach. Carcinoma of the stomach was suspected. Surgical exploration revealed a large chronic ulcer on the lesser curvature, and a resection was performed. The lesion measured 4 cm. in diameter; the edges were sloping, and the base was firm and fibrous. This patient has survived for three and one-half years.

Case 6. A 72 year old Scottish farmer was admitted with a history of epigastric distress for five years, tiredness, loss of weight and occasional vomiting for two weeks. The pain occurred about three hours after meals and was relieved by food and soda. Gastric analysis showed free hydrochloric acid. Roentgenologic examination showed a lesion in the pyloric region, with evidence of gross gastric retention. After a course of lavage and intravenous feedings, operation was carried out and a resection

performed. The ulcer was noted on the lesser curvature, measured 3 cm. in diameter and revealed firm margins and indurated base. This patient has survived for five and one-half years.

Case 7. A 62 year old Scottish locomotive works employee entered hospital with complaints of recurrent epigastric burning sensation for 20 years and recurrent tarry stools for seven months. His pain occurred one-half to two hours after meals. He obtained very little improvement on restricted diets. Roentgenologic studies on two occasions were pronounced negative. Vomiting, which was not marked early in his illness, became progressively more pronounced. More recently he had lost some weight and passed tarry stools. Gastric analysis revealed the presence of free hydrochloric acid. On admission he was quite dehydrated and vomited continually. Intravenous therapy and gastric lavage improved his general condition. At operation, a week later, a prepyloric ulcer was found on the anterior wall of the stomach, and a resection was performed. The lesion measured 1.2 cm. in diameter and penetrated deeply into the wall. There were marked surrounding inflammatory changes present. This patient, although apparently free of metastases at operation, died of his disease after four and one-half years.

Case 8. A 36 year old white male was admitted with a history of intermittent epigastric pain of three years' duration. The attacks occurred after meals but were not associated with vomiting. He passed tarry stools on several occasions. Gastric analysis was not performed. Roentgenologic examinations failed to demonstrate any organic lesions, but pylorospasm was reported. At operation an ulcer was found on the greater curvature, and a resection was carried out. The lesion measured 2.5 cm. in diameter and was situated 2 cm. from the pylorus. The edges were raised and the floor was necrotic. This patient has survived for a period of six years.

Case 9. A 57 year old housewife entered hospital after an illness of six months' duration. Her complaints were pain and tenderness in the epigastrium, anorexia, some loss of weight and, more recently, passage of tarry stools. Gastric analysis revealed a low total acidity and no free hydrochloric acid. Roentgenologic examinations were never carried out. At operation a subtotal gastrectomy was performed. The lesion was located 10 cm. from the pylorus. The ulcer was 2 cm. in diameter and 0.5 cm. in depth, and its base was thickened. Two weeks postoperatively the patient died of peritonitis due to a ruptured duodenum.

Case 10. A 48 year old salesman entered hospital with complaints of flatulence and epigastric pain intermittently for 17 years. His attacks occurred two hours after meals. Diet and antacids afforded some relief. Gastric analysis had not been carried out. Roentgenographic examination revealed a duodenal ulcer. More recently (during the two months before admission) he had vomited occasionally. At operation a prepyloric ulcer was found and a resection performed. The ulcer measured 2 cm. in diameter and penetrated quite deeply into the wall. The edges were raised but not indurated. This patient has survived for 15 years postoperatively.

Analysis of Clinical Findings

Sex: Eight of the cases occurred in males and two in females. In this small series, therefore, cancer on ulcer occurred four times as frequently in males as in females.

Age: The patients varied in age from 36 to 72 years, with an average age of 55.4 years. Fifty per cent of the patients were over 50 years of age. Ninety per cent of the cases occurred in patients over 40 years of age. The average age at the onset of symptoms was 48.3 years.

Duration of Symptoms: The symptoms referred to are those classically recognized in the ulcer syndrome. The patients had a proved ulcer or were strongly suspected clinically of having an ulcer and came under treatment for the condition. Two cases gave a history of 20 years' and 17 years' duration, respectively. The shortest history obtained was of six months' duration. Two cases had a duration of five years. One case gave a history of "several years." In the remaining four cases the duration of symptoms varied from two to three years. The average duration in the entire group of cases was six and three-tenths years. It is interesting in this respect to note Boyd's [4] comment: "Benign ulcers as a rule have a long history of gastric trouble, whilst the cancer cases have a remarkably short one and give no previous history of gastric trouble."

Hemorrhage: A history of bleeding was obtainable in six cases, or 60 per cent of the group. In one of these, massive hematemesis necessitated an emergency operation. In the other five cases, evidence of hemorrhage consisted of vomiting of coffee-ground material, melena or positive tests for occult blood in stools or gastric contents. In the remaining four cases (40 per cent) no such history or positive laboratory tests were obtained.

Free Acid: Anacidity was found in two cases of the series (20 per cent). In four instances free hydrochloric acid was demonstrated in normal or greater than normal amounts. The test was not performed in three patients (in one of these because of massive hematemesis), and no record of any free acid determination was found in the remaining case.

Roentgen-Ray: Conclusive roentgenographic evidence of ulcer was demonstrated in seven cases (70 per cent) in this group. In two of the cases x-ray studies were attempted but never satisfactorily showed the presence of ulcer. In one no such examination was carried out.

Endoscopic and Cytological Studies: None of the patients in this group had either gastroscopic examination or cytologic studies for malignancy, so that no assistance could be derived from these procedures. In this connection, Kiernan [9] feels that the gastroscopist is second in importance only to the roentgenologist in the diagnosis of gastric lesions, especially in visualizing lesions of the cardia and upper third of the posterior wall of the stomach, areas not well seen by x-ray. He states, however, that gastroscopic differentiation of the benign from the malignant gastric ulcer is dangerous, for it is often impossible for even the pathologist to distinguish the two by gross examination of the resected specimen.

Operation: In each instance a subtotal gastrectomy was carried out, with such modification as the individual circumstances dictated.

Site of the Lesion:

Lesser curvature	5
Prepyloric	3
Posterior wall	1
Greater curvature	1

The majority of these cases (60 per cent) occurred on the lesser curvature and posterior wall, i.e., where chronic peptic ulcers most frequently are located. In three instances (30 per cent) the lesion was located in the prepyloric region, which is regarded as a suspicious area in which ulceration is prone to be malignant, regardless of size.

Size of the Lesion: The largest ulcer (lesser curvature) in this group measured 5.5 cm. in diameter. The smallest lesion (prepyloric) measured 1.2 cm. in diameter. It is interesting to note that the patient who gave the longest clinical history in this group (20 years) had the smallest ulcer. The case with the next longest history (17 years) had a lesion only 2 cm. in diameter. The average size in the series was 2.9 cm. in diameter.

Metastases: The pathologic diagnosis in nine instances was adenocarcinoma, and in one instance, carcinoma solidum. In four cases (40 per cent) metastases were already present in the regional lymph nodes at operation. In the remaining six cases no metastatic growth was demonstrated in the nodes or at any other site. In the cases in which metastases were present, the average size of the ulceration was 3.5 cm., while in those cases in which metastases were not found the average lesion measured 2.5 cm. in diameter. Of the lesions that measured over 2.5 cm. in diameter, 40 per cent revealed the presence of metastases in the regional lymph nodes.

Preoperative Diagnosis: In five instances a preoperative diagnosis of benign gastric ulcer was made, malignancy being neither considered nor suspected. In one case a diagnosis of cancer was considered in view of a familial history of malignancy, the patient's mother having died of carcinoma of the stomach. In two patients gastric ulcer was diagnosed, but malignancy was favored because the lesion had failed to heal under medical treatment and achlorhydria was present. Another case was suspected of malignancy because of the roentgenographic appearance of the lesion. In the remaining case a diagnosis of cancer was made because of a history of weight loss and from the roentgenographic findings.

Subsequent Course: There was one immediate operative mortality (case 9) in the group. Death occurred from peritonitis two weeks after operation due to duodenal leakage. Another patient (case 2) survived the operation but died three months later with recurrence of the tumor and carcinomatosis. It is interesting that this patient's mother also died of cancer of the stomach. Another patient (case 1) died of his disease one year postoperatively. In each of the above three instances metastases were already demonstrable at the time of operation. Case 7 died of his disease after four and one-half years' survival. This patient had no apparent metastases at operation. The six remaining patients are alive and well at present. In one of these (case 3) metastases were present in lymph nodes at operation. The survival periods are as follows: case 3, three and one-half years; case 4, one and one-half years; case 5, three and one-half years; case 6, five and one-half years; case 8, six years; case 10, 15 years.

Discussion

In this series of 10 cases in which examination of the resected stomach showed histologic changes that conform to the criteria for the diagnosis of cancer on ulcer, it is of course appreciated that the number is too small for the results of the analysis of clinical findings to be statistically significant. It is of some interest, however, to compare them with known facts derived from larger series in which benign gastric ulcer or malignancy was present.

As to sex, it is generally held that both benign peptic gastric ulcer and carcinoma are about twice as common in males as in females, although Herbut [7] states that the benign lesion is found in males in 88 per cent of cases. No doubt the ratio is somewhat higher for the benign as compared to the malignant lesion. In our cases, where ulcer is believed to have preceded the development of cancer the ratio is 4 to 1. In our series, the average age of 54.6 years, with 90 per cent of the cases over 40, is in agreement with recognized figures for the age incidence of the development of malignancy in this organ.

The fact that two of our cases of cancer on ulcer gave histories of duration of symptoms of 20 and 17 years, respectively, has raised the average to the rather high figure of six and three-tenths years. It is noteworthy, however, that all but one were over two years and the majority considerably longer. While it is possible carcinoma in situ could have existed quiescent for such long periods, the ordinary infiltrating form of cancer would not be likely to do so. These figures therefore tend to support the presence of an initially benign lesion.

Hemorrhage as a point of differential diagnosis between these two conditions is not particularly helpful. Massive hemorrhages are no doubt more common in benign ulcer, but simple bleeding is equally frequent in both. LaDue [12] states that massive hemorrhage occurred in only 6 per cent of a series of 1,000 patients with gastric malignancy, while it is reported that it is met with in from 20 to 40 per cent of benign ulcers. In only one of our series was the hematemesis sufficiently severe to necessitate emergency operation. Signs of bleeding, however, were reported in six of the 10 cases.

In contrast to hemorrhage, the degree of acidity of the gastric juice is of considerable, though not positive, diagnostic value in the differentiation of these lesions. Anacidity may occur in benign ulcers (7.4 per cent of LaDue's [12] series of 81 patients), but it is an accepted rule that the greater the amount of acid the less likely the lesion is to be malignant. Of the six of the above cases in which this test was done, two showed absence of acid, while in four it was present in normal or greater than normal amounts. These figures indicate a tendency to higher degrees of acidity in cancer on ulcer than in the usual forms of malignancy.

The site and size of the ulcer are of considerable importance. For pur-

poses of location, and that there may be no overlapping, we divide the whole lesser curvature from esophageal to pyloric orifice into three parts. The proximal inch is included under cardia and the distal inch and a half under prepyloric area, while ulcers located in the middle portion are considered on the lesser curvature. Of course, both the cardiac and prepyloric areas include, in addition, the whole circumference of the stomach at those sites. It is an accepted rule that benign ulcers are more common on the lesser curvature and cancer on the greater curvature, though the figures obtained by various authors differ considerably. Benedict [12] gives the following ratios: lesser curvature, 75 to 25; greater curvature, 2 to 98; prepyloric and cardiac areas, 50 to 50. Six of the 10 cases in our series showed the cancer on ulcer to be located in areas where benign lesions predominate, and three of the four remaining in the prepyloric region, where the ratio is equal. This would indicate a tendency for this type of lesion to occur in the areas where benign ulcers are in the majority.

As to size, smaller ulcers are more often benign and larger ulcers malignant. The point of diameter where they are equal is about 3 cm. In our experiences, however, there is no positive limit to the size of gastric peptic ulcers. We encounter many large ones, well over 4 cm. In this series six of the 10 ulcers were under 3 cm. in diameter and only three were above, again showing a tendency for cancer on ulcer to fall into the benign group. Metastases to regional nodes were inclined to occur in the cases with larger ulcers.

Follow-up of a large group of cases, including all types of carcinoma of the stomach treated by resection at the Royal Victoria Hospital, shows a five year survival in approximately 20 per cent. The results in this series of cancer on ulcer are distinctly better. Sixty per cent are alive and well, though not all are five years postoperative. Three of the four patients who died showed metastases at the time of resection. The other case in which the lymph nodes were involved has survived three and one-half years.

An investigation of the problem as to whether any or all of these cases of cancer on ulcer actually originated as a carcinoma in situ, with subsequent peptic ulceration, could not be undertaken from the evidence at hand. Unfortunately, the gross material had not been preserved and hence was no longer available. Moreover, clinical histories are not particularly helpful in settling this question, as it is believed cancer in situ can exist as such for many years before actual invasion develops. It is an interesting idea, and all future cases showing the exact histologic changes of cancer on ulcer should be thoroughly studied from this standpoint. Possibly this will reveal carcinoma in situ of the stomach to be a more common lesion than is now supposed. It is strange, however, if such is the case, that it has not been recognized in autopsy material from time to time in the past.

Conclusions

An analysis is reported of the clinical histories of 10 cases in which histologic examination of the resected stomach revealed a lesion conforming to the criteria for the diagnosis of cancer on ulcer.

It showed an incidence of four males to one female, and an average age of 54.6 years. The average duration of gastric symptoms was six and three-tenths years. Severe hemorrhage was present in one case, and signs of bleeding in five other cases. Anacidity was found in two cases, and normal or higher than normal acid in four of the six cases in which this test was done. Examination of the resected stomach as to location and size of the ulcer revealed a majority of the lesions to fall into the predominantly benign groups. Sixty per cent of the cases are alive and well, compared to approximately 20 per cent five year cures in all cases having resection of the stomach for cancer.

BIBLIOGRAPHY

1. Askanazy, M.: Über Bau und Entstehung des chronischen Magengeschwürs sowie Soopilzbefunde in ihm, Virchows Arch. f. path. Anat. **234**: 111, 1921; **250**: 370, 1924.
2. Borrmann, R., *in* Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, 1926, Julius Springer, Berlin, IV, 812.
3. Bowen, J. T.: Precancerous dermatoses, J. Cutan. Dis. **30**: 241, 1912.
4. Boyd, W.: Surgical pathology, 1946, W. B. Saunders, Philadelphia.
5. Broders, A. C.: Carcinoma in situ contrasted with benign penetrating epithelium, J. A. M. A. **99**: 1670, 1932.
6. Ewing, J.: Neoplastic diseases, 1930, W. B. Saunders Company, Philadelphia.
7. Herbut, P. A.: Surgical pathology, 1948, Lea & Febiger, Philadelphia.
8. Hertig, A. T., Sommers, S. C., and Bengloff, H.: Genesis of endometrial carcinoma. III. Carcinoma in situ, Cancer **2**: 964, 1949.
9. Kiernan, P. C.: Gastric ulcer and its relation to malignancy, S. Clin. North America **30**: 1743, 1950.
10. Mallory, T. B.: Carcinoma in situ of the stomach and its bearing on the histogenesis of malignant ulcers, Arch. Path. **30**: 348, 1940.
11. Newcomb, W. D.: The relationship between peptic ulceration and gastric carcinoma, Brit. J. Surg. **20**: 279, 1932-33.
12. Pack, G. T., Moderator: Panel Discussion, The relationship of gastric cancer, Cancer **3**: 515, 1950.
13. Schiller, W.: Untersuchungen zur Entstehung der Geschwülste. 1 Teil: Collum carcinoma des Uterus, Virchows Arch. f. path. Anat. **263**: 279, 1927.
14. Wilson, L. B., and MacCarty, W. C.: The pathological relationship of gastric carcinoma, Am. J. M. Sc. **138**: 846, 1909.

OBSERVATIONS ON THE SPLENIC FLEXURE SYNDROME *

By THOMAS E. MACHELLA, M.D., F.A.C.P., *Philadelphia, Pennsylvania,*
HARVEY J. DWORKEN, M.D., *Shaker Heights, Ohio* and
FRUCTUOSO J. BIEL, M.D., *Concepcion, Chile*

DURING the past several years we have seen a number of patients because of chest pain and other manifestations which led their physicians to suspect or even to diagnose coronary artery disease. The symptoms were due to a non-coronary cause, namely, the "splenic flexure syndrome." A few of the patients had been living the lives of cardiac invalids, retired from useful occupations and with activities markedly restricted. A number of them were sent by their physicians to the Cardiac Section, where no cardiac lesion was found. They were then referred to us for evaluation from a gastrointestinal standpoint. Fluoroscopic examination of the abdomen of some of these patients during attacks of precordial pain revealed a collection of gas in the splenic flexure. This finding suggested that distention of the splenic flexure by gas, or at times possibly by feces, might be responsible for the symptoms.

Thus far, a group of 19 male and 21 female patients with the symptom complex has been observed. It is the purpose of this communication to present an analysis of the clinical picture and the circumstances believed responsible for its production. The average age of the subjects was 46 (29 to 73 years) (table 1).

CLINICAL AND ROENTGEN CHARACTERISTICS

1. Location of Pain and Discomfort: During an attack, pain or discomfort was experienced in more than one site in 80 per cent of the 40 cases. It was experienced in only one area in 20 per cent; in two separate areas in 27.5 per cent; in three in 27.5 per cent; in four in 12.5 per cent; in five in 10 per cent, and in six in 2.5 per cent (table 1).

The discomfort occurred in the left upper quadrant of the abdomen in 75 per cent; in the left flank in 27.5 per cent; in the precordial area in 75 per cent; in one or both shoulders in 25 per cent; in the left side of the neck in 20 per cent; in one or both arms in 20 per cent; and in other sites (the left scapula, the interscapular area, both sides of the chest, the epigastrium, the xiphoid area, the jaw and the ulnar side of the left hand) in 30 per cent (table 1).

* Presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 22, 1952.

From the Gastro-Intestinal Section, Kinsey-Thomas Foundation, of the Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia, Pa.

2. Nature of the Discomfort: The nature of the discomfort varied a great deal (table 2). The most frequent sensation in the left upper quadrant was that of distention, pressure or fullness; in the precordial region, that of pressure, fullness or an ache. In the sites of reference such as the shoulder, neck or arm it was described as an ache or a pain, occasionally burning in

TABLE I

Sites of Pain or Discomfort

Case	Age/Sex	Left Upper Quadrant	Left Flank	Precordium*	Shoulder	Left Side of Neck	Arm	Other
1	45/M	+	+	+	Left		Left	Left hand
2	48/M	+		+				
3	56/F	+		+		+		Left jaw
4	46/F	+		+		+		
5	73/F	+		+		+		
6	67/F	+		+				Left scapula
7	39/F	+		+				Interscapular area
8	53/F	+		+		+	Left	
9	45/F	+		+	Both			
10	45/M	+	+	+	Left			
11	43/F	+	+	+		+		Interscapular area
12	37/M		+	+				
13	35/F		+	+				
14	55/M			+	Left	+		
15	46/M			+				
16	60/M			+				
17	53/M			+				
18	44/F	+		+	Left		Left	
19	34/F	+		+	Left		Left	
20	49/M	+		+				Interscapular area
21	48/F	+		+		+		
22	32/F	+		+				
23	29/F	+		+				
24	40/F	+	+	+	Left		Left	
25	30/M	+		+				Epigastrium
26	44/M	+		+				
27	45/F			+				Left scapula
28	52/M	+			Left	+	Both	
29	40/F	+						Both sides of chest
30	44/F	+		+				Xiphoid
31	57/F	+	+					
32	40/M	+	+					
33	57/M	+	+					
34	50/F	+						
35	46/F	+		+				
36	37/F	+						
37	42/F	+	+	+	Left			Interscapular area
38	55/M		+					
39	48/F							Left scapula
40	32/M				Left			

* Cases 1 to 19 were suspected of having coronary artery disease by their physicians.

character. The degree of severity of the pain was not very great in any instance.

Symptoms, other than pain, included palpitation, shortness of breath, a sensation of choking, substernal oppression and apprehension. These, when associated with pain in the precordial area, were rather alarming to

TABLE II

Characteristics of the Discomfort as Described by Patients

Case	Nature of Discomfort	Precipitating Factors* and/or Time of Occurrence	Relief by†
1	Burning pain	Constipation, certain foods; 1 to 2 hrs. after meals	Expulsion of flatus, effective laxative
2	Dull ache	3 to 4 hrs. after meals; night and weekends	Expulsion of feces or flatus
3	Dull pain	Constipation; day or night	Enema, expulsion of feces or flatus
4	Pressure, ache	Constipation; night	Expulsion of feces or flatus, whiskey
5	Distention, substernal smothering	Constipation; night	Expulsion of flatus
6	Ache	Constipation; constant	Bowel movement
7	Dull ache	Day	Expulsion of flatus, belching
8	Spasm, ache	Nervous strain; day	Expulsion of flatus, belching
9	Fullness, pressure	Meals; night	Expulsion of flatus, belching
10	Sharp, distending	Right after meals	Expulsion of flatus
11	Pressure, distention	Meals	Expulsion of feces or flatus
12	Dull ache	Emotional disturbances; night	Expulsion of flatus
13	Pain	Emotional disturbances; day	Eating
14	Dull ache	1 hr. after meals	Expulsion of flatus
15	Dull ache	Emotional disturbances; walking about	Effective enema, lying down to rest
16	Oppression	Emotional disturbances; night	Expulsion of flatus or belching
17	Heart hurts	Emotional disturbances	Expulsion of flatus or bending over
18	Severe pain like gas	While in bed	Expulsion of flatus
19	Pressure pain	Emotional disturbances	Bowel movement, effective enema
20	Pressure and fullness	Lying down; evenings and nights	Expulsion of flatus, belching
21	Distention, ache	Lying down; nights	Sitting up
22	Fullness	Nervousness, eating, passage of stool	Expulsion of flatus, belching
23	Severe burning or grabbing pain	Nervousness, constipation; any time	Effective enema
24	Distention and pain	Emotional disturbance	Eating
25	Pressure	Lying down after meals	Sitting up, expulsion of flatus, belching
26	Pressure	Going out on street by himself	Expulsion of feces or flatus
27	Fullness, ache	Aggravation	Expulsion of flatus, belching
28	Pain	Lying down, constipation	Expulsion of flatus, belching
29	Pressure	Nervousness	Expulsion of flatus, belching
30	Gas pain	—	Expulsion of flatus
31	Distention, cramp	Constipation; day	Lying down
32	Sharp ache	Emotional disturbances; night	Expulsion of flatus, belching, eating
33	Gas pain	Before meals	Expulsion of flatus, belching
34	Dull distention	Meals; night	Expulsion of flatus, feces
35	Swelling	Eating heavy meals, working hard	Expulsion of flatus, belching
36	Constriction pain	Constipation; day	Sitting up, belching, diarrhea
37	Burning pain	Menstrual periods, nervousness	Expulsion of flatus, feces
38	Gas pain	Constipation	Expulsion of flatus or feces
39	Sharp ache	Emotional disturbances; night	Expulsion of flatus or feces
40	Distending ache	In bed at night	Expulsion of flatus or feces

* All patients admitted emotional disturbances except cases 1, 6, 34 and 36.
† All patients complained of constipation except cases 7, 12 and 32.

the patient because of the possibility that they were caused by a cardiac lesion.

3. Precipitating Factors: The factors or circumstances which were mentioned by the patient as precipitating the symptoms were: emotional dis-

TABLE III

Roentgenological Characteristics of Colon and Reproduction of Symptoms

Case	Diagnosis or Comment of Radiologist on	"Trap" Arrangement of Splenic Flexure	Air Present in Splenic Flexure on Fluoroscopy	Reproduction of Discomfort by Balloon Distention of Splenic Flexure
1	Nothing abnormal seen	+	+	
2	Irritability of sigmoid	+	+	+
3	Sigmoid spasm	+	+	
4	Atonic	+	+	
5	Negative	+		
7	Negative	+		
8	Spasm of descending colon	+	+	+
9	Increased tone	+		
10	Nothing abnormal seen	+		
11	Negative	+		+
12	Negative	0		
13	—	?	+	
14	Negative	+	+	
15	Spastic colon	+		
16	Increased tone in sigmoid	?	+	
17	Symptoms reproduced	+	+	
18	Spastic colon; symptoms reproduced	0		
19	Symptoms reproduced	+		+
20	Polyp of sigmoid	?	+	
21	Smooth descending colon	+	+	
22	Negative	+		
24	Negative	+		+
25	Negative; symptoms reproduced	+		
26	Nothing abnormal seen	+		+
27	Negative	+	+	
29	Spastic colon	+		
30	Negative	+	+	+
31	Negative	0		
32	Negative	+		
33	Spastic colon; symptoms reproduced	+		
34	Spastic colon	+		
35	—	?		+
36	Increased tone of sigmoid	+		
37	Spasm of descending colon	+		
38	Negative; symptoms reproduced	+		
39	Negative	+	+	
40	—	?	+	+

turbances in 37.5 per cent, constipation in 25 per cent, meals in 25 per cent and lying down in 12.5 per cent (table 2). Significant emotional motivating factors, however, were admitted by all except cases 1, 6, 34 and 36. Constipation was present in all except cases 7, 12 and 32. The discomfort occurred in some during the day, in others at night.

4. Relief from Discomfort: Relief from discomfort was attributed to the expulsion of feces or flatus spontaneously or as the result of an enema in 36 of the 40 cases (table 2). Relief was also ascribed to the ingestion of meals in two instances (cases 13 and 24), to sitting up in three (cases 21, 25 and 36), to lying down in two (cases 15 and 31), and to bending over in one (case 17). One patient (case 19) reported no relief from nitroglycerin.

5. Presence of Gas in Splenic Flexure During Discomfort: The abdomens of 15 of the patients were examined fluoroscopically during periods

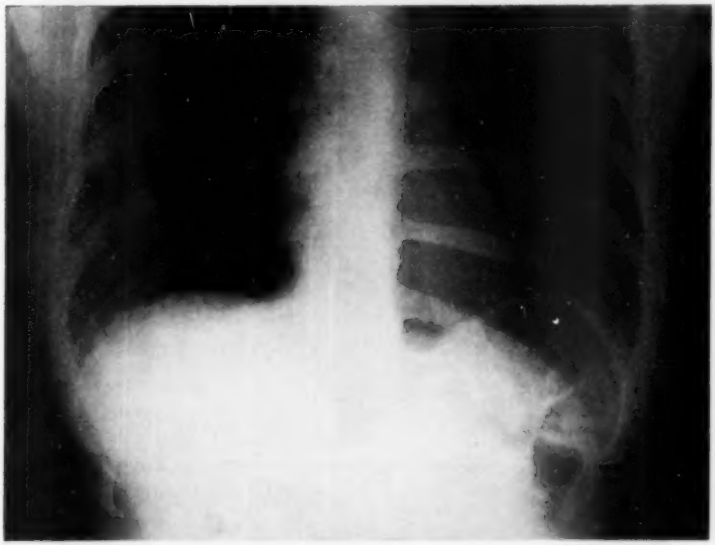


FIG. 1. Presence of air in splenic flexure of colon on scout film of abdomen during period of symptoms (case 11).

of discomfort. In each instance (table 3) an accumulation of gas was seen in the splenic flexure (figure 1). One of them (case 20), examined during a fairly severe attack, was observed to have the left dome of the diaphragm displaced upward into the left chest by an enormous gas-distended splenic flexure. A plain film of the abdomen taken about an hour later and after he had expelled some flatus revealed that the left diaphragm was still elevated, though less so than previously. Some gas was still present and the degree of discomfort was much less than prior to passage of flatus. Another patient (case 1) was repeatedly observed to have gas in the splenic flexure during periods of discomfort but not during asymptomatic intervals.

6. Roentgenologic Characteristics of Colon: The colon was examined by barium enema in 34 of the 40 patients by various members of the Radiology Department for the purpose of excluding organic disease (table 3). The examination was reported as "negative" or "nothing abnormal seen"

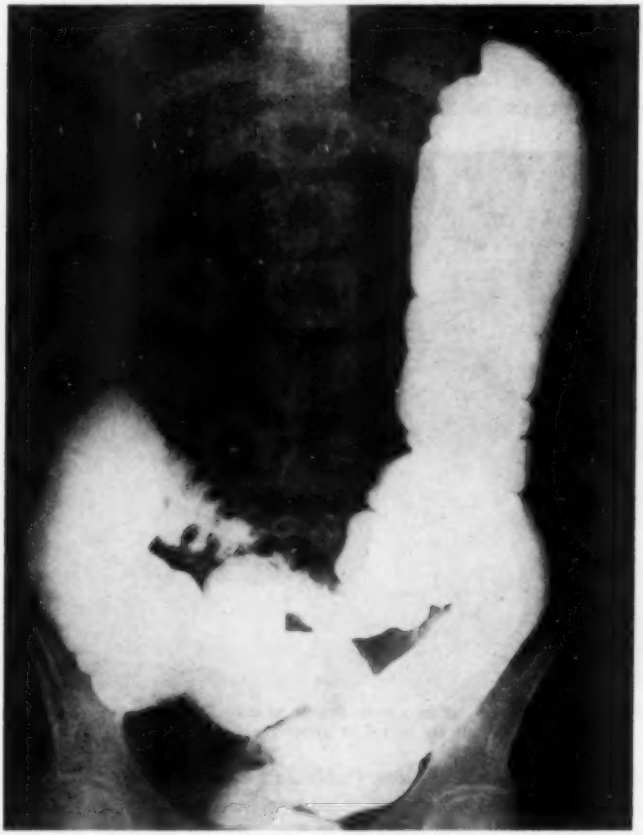


FIG. 2. Roentgen appearance of colon following introduction of barium-water mixture by rectal enema. Note the "traplike" arrangement of distal transverse colon and the descending colon (case 19).

in 19; as showing "spasm" or "irritability" of the sigmoid or other parts of the colon in 11, and as showing "increased tone" in one instance. In one patient (case 4) the colon was reported as "atonic"; however, marked spasm of her sigmoid was encountered during sigmoidoscopy. In six of the patients (cases 17, 18, 19, 25, 33 and 38) the roentgenologist reported that

symptoms were reproduced by the introduction of the barium mixture into the colon.

Inspection of the available roentgen films of the colon in 32 cases revealed that the distal transverse colon and the descending colon formed a very acute angle at the splenic flexure in 29 instances (figure 2), an anatomic arrangement which could serve as a trap for gas or feces under appropriate circumstances. In 27 of the 29, the rib level to which the tip of the splenic flexure of the barium filled colon extended beneath the costal margin with the patient in the prone position was the ninth in two, the tenth in 13, the eleventh in 10, and the twelfth in two. In the remaining two cases it was not possible to determine the level because the tip of the

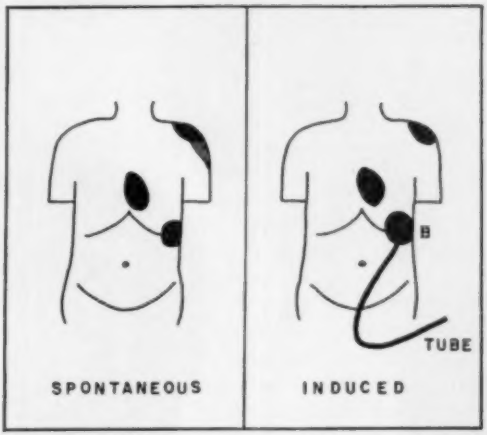


FIG. 3. Areas in which pain was experienced during a spontaneous attack as compared to the areas of discomfort associated with air-inflation of a balloon introduced into the splenic flexure. In the induced episode the pain in the shoulder did not extend down the arm as it did in the spontaneous attack (case 19).

splenic flexure was off the film. The barium did not enter the terminal ileum in three of the 27 cases.

7. Reproduction of Discomfort by Inflation of a Balloon in the Splenic Flexure: The air inflation of a rubber balloon introduced into the splenic flexure by means of a tube containing a coiled spring, as used by Kern, Almy and Stolk,[1] reproduced the symptoms (figure 3) in each of the nine patients in whom intubation was successfully accomplished (table 3). The amount of air required to reproduce the symptoms varied from 165 to 665 ml.

COMMENT

In articles describing functional disturbances and anomalies of the colon it has been stated that an accumulation of gas in the splenic flexure was

capable of producing discomfort in the chest or precordial region.[2, 3, 4, 5, 6] Distention of the splenic flexure by air inflation of a balloon following oral intubation has been reported [7, 8] to produce discomfort at the site of the distending balloon. The finding of a considerable amount of air in the

FIG. 4. Presence of gas in splenic flexure of colon and in fundus of stomach. Partial relief from the discomfort due to distention of the splenic flexure by belching is sometimes experienced by the patient.

splenic flexure during the period of symptoms and the reproduction of symptoms by air inflation of a balloon in that area indicate that distention of the splenic flexure can give rise to discomfort not only at the site but also in areas of the upper body to which coronary pain may be referred.

The splenic flexure is ideally constructed to serve as a trap for the col-

lection of air or feces in most individuals. It is situated higher and more nearly posterior than the hepatic flexure and may or may not rest against the diaphragm, depending upon the degree of its distention and upon that of the stomach.[9] The "traplike" arrangement was present in most of our patients with the splenic flexure syndrome, but it also occurred as frequently in a control group of patients whose barium enema films were selected at random from a teaching file collection representing miscellaneous conditions of the colon. That the anatomic arrangement is not alone responsible for the manifestations is evidenced, however, by the fact that at least three of our patients (cases 12, 18 and 31) did not have such an appearance demonstrable on the barium enema films. This means that other factors must be operative to produce sufficient distention of the splenic flexure to give rise to symptoms.

One such factor should constitute a hindrance to the forward progress of material through the splenic flexure and should be present only at times. The absence of roentgen evidence of organic obstruction, the frequent roentgen demonstration of spasm of the descending colon or sigmoid, the susceptibility of the sigmoid and descending colon to spasm during emotional storms strongly suggest that the hindering factor is one of spasm. This is further supported by the fact that the symptoms are often precipitated by emotional factors, and that relief is afforded by expulsion of feces or flatus. For distention of the splenic flexure to occur spontaneously, there should be, in addition to an obstructing element distally, a potent propulsive force proximal to the splenic flexure. This could be in the nature of increased motor activity or tonicity of the proximal colon and possibly the distal ileum. Increased motor activity of both of these areas can be incited by emotional disturbances, as well as by the ingestion of meals. It will be recalled that the symptoms were precipitated by the ingestion of meals in about 25 per cent of our cases.

The relief from symptoms by eating, in two instances, is not incompatible with the above explanations. Ingestion of a meal, by exciting the gastrocolic reflex, could very well evacuate "trapped" content from the splenic flexure, if the force were sufficient to overcome spasm in the descending colon or sigmoid.

In some cases the occurrence of symptoms at night was attributed to lying down. Careful inquiry in such instances usually revealed that at such times disturbing emotional influences were operating. In others, relief from symptoms by lying down can be explained by the relaxation afforded by the removal of the patient from tense emotional situations. The partial relief afforded by belching can in part be explained by the lessening of tension in the splenic flexure as a result of expulsion of air from the fundus of the stomach (figure 4).

The importance of proper recognition of the symptom complex lies not so much in the actual severity of the symptoms as in the fact that their oc-

currence may be wrongly ascribed to serious cardiac disease. The relief of symptoms by expulsion of flatus or feces furnishes a useful clue to their probable cause.

Summary and Conclusions

1. In a group of 40 patients, a symptom complex was evaluated consisting of pain or discomfort in one or more of the following sites: the left upper quadrant of the abdomen, the precordial area, chest, left shoulder, neck or arm, in some instances associated with a sensation of choking, shortness of breath, palpitation and apprehension.

2. The symptoms, in the majority of instances, were precipitated by emotional disturbances, were associated with constipation, and were relieved by the expulsion of flatus or feces.

3. Evidence that the symptoms were caused by distention of the splenic flexure consists of the visualization of gas in that area during symptoms, the absence of gas during asymptomatic intervals, and the reproduction of symptoms by distention of the splenic flexure by air inflation of a balloon introduced through the rectum.

4. It is believed that the symptom complex is a manifestation of spastic colon, and that its recognition and appreciation are important in the differential diagnosis of disease of the coronary arteries.

BIBLIOGRAPHY

1. Kern, F., Jr., Almy, T. P., and Stolk, N. J.: Effects of certain antispasmodic drugs on the intact human colon with special reference to Banthine, Am. J. Med. **11**: 67, 1951.
2. Kantor, J. L.: Functional disturbances of the colon, *in* Portis, Diseases of the digestive system, 1944, Lea and Febiger, Philadelphia, Chapter 26, pp. 554–562.
3. Seward, C.: The diagnosis and treatment of spastic colon, Med. Press **217**: 289, 1947.
4. Jordan, S. M.: Colonic dysfunction, New York State J. Med. **49**: 1802, 1949.
5. Collins, E. N.: Functional indigestion, Pennsylvania M. J. **55**: 21, 1952.
6. Bockus, H. L.: Gastroenterology, 1944, W. B. Saunders Co., Philadelphia, Vol. II, p. 394.
7. Jones, C. M., and Pierce, F. D.: The mechanism and reference of pain from the lower intestinal tract, Tr. A. Am. Physicians **46**: 311, 1931.
8. Jones, C.: Digestive tract pain, 1938, Macmillan Co., New York.
9. Piersol, G. A.: Human anatomy, 1907, J. B. Lippincott Co., Philadelphia.
10. Alvarez, W. C.: An introduction to gastroenterology, 4th Ed., 1948, Paul B. Hoeber, New York, p. 675.

LATENT STEATORRHEA *

By Douglas G. Cameron, M.D., E. H. Bensley, M.D., F.A.C.P., and Phyllis Wood, B.Sc., *Montreal, Canada*

During the past two years we have found idiopathic steatorrhea in eight adults, none of whom had bowel symptoms to suggest the diagnosis. It seems reasonable to refer to the disorder as latent steatorrhea. These individuals presented with one or more of the following conditions: tetany, frank osteomalacia, unexplained megalocytic anemia and iron deficiency. Steatorrhea was demonstrated in each case by careful fat balance studies. Celiac disease without diarrhea was described in children in 1923.[1] Since then, steatorrhea in adults without bowel symptoms has been mentioned incidentally by several authors.[2, 3, 4, 5, 6, 7] However, latent steatorrhea has not received the attention it deserves and it seems likely that the condition often goes unrecognized.

Description of Cases

The presenting symptoms and their duration, together with the sex and age of each patient, are shown in table 1. There were five females and three males, and their ages ranged from 18 to 57 years. Three presented with tetany, one with megalocytic anemia and tetany, one with bone pain, one with bone pain and deformity, one with unexplained megalocytic anemia and one with unexplained iron deficiency. Symptoms had been present for from two to 48 months, with an average duration of 21 months, before coming under our observation. None of the patients had lived in the tropics. Seven were native-born Canadians whose only foreign travel had been visits to the neighboring northern states of the United States. One was a naturalized Russian immigrant who had lived continuously in Canada for 24 years before the onset of symptoms. A clear history of celiac disease in childhood was not obtained from any of the patients. Six denied gastrointestinal symptoms in general, and diarrhea or pale, bulky, frothy, foul smelling stools in particular. Two gave a history of occasional watery diarrhea, but on direct questioning neither recalled that stools had ever been pale, bulky, frothy or especially offensive. Moreover, these classic features of the stool in idiopathic steatorrhea were not apparent on casual inspection of the feces in any of our cases.

The salient clinical and laboratory findings are shown in tables 2 and 3.

* Presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 22, 1952.

From the Departments of Medicine and Metabolism of the Montreal General Hospital and the Department of Medicine, McGill University, Montreal.

This work was done with the aid of a grant from the National Research Council, Canada.

TABLE I

Presenting Conditions

Case	Age	Sex	Presenting Conditions	Duration of Symptoms (Months)
1	56	Male	Megalocytic anemia	3
2	45	Female	Frank osteomalacia with bone pain	12
3	56	Male	Iron deficiency anemia	36
4	38	Female	Hypocalcemic tetany	24
5	39	Male	Hypocalcemic tetany	48
6	18	Female	Late rickets with bone pain and deformity	24
7	57	Female	Megalocytic anemia and hypocalcemic tetany	15
8	28	Female	Hypocalcemic tetany	2

CASE REPORTS

Case 1. A 56 year old man presented with severe megalocytic anemia (red blood cells, 2.1 million per cubic millimeter; hemoglobin, 7.8 gm. per 100 ml.). A sternal puncture showed megaloblastic bone marrow. The patient had a smooth red tongue. There was no neurologic abnormality. Free HCl was present in the gastric juice, and the prothrombin time (38 seconds, Quick) was elevated.

Case 2. A 45 year old woman complained of severe pain in the ribs, back and hips. She had degree IV osteomalacia.[8] The serum calcium (8.4 mg. per 100 ml.) and the serum inorganic phosphorus (2.2 mg. per 100 ml.) were low. The serum alkaline phosphatase (17 King and Armstrong units per 100 ml.) was elevated. X-ray examination showed general decalcification of the skeleton, with pseudofractures of the left scapula, both ischial rami and the seventh left rib and twelfth right rib. The prothrombin time (25 seconds) was elevated. There was no evidence of renal disease.

Case 3. A 56 year old man presented with severe iron deficiency anemia (red blood cells, 2.1 million; hemoglobin, 5.1 gm.; serum iron, 13 γ per 100 ml.; unsaturated iron binding capacity, 450 γ per 100 ml.). There was no history of blood loss and no evidence of occult bleeding. Extensive radiologic and endoscopic investigation failed to demonstrate any lesion in the gastrointestinal tract. Free HCl was present in the gastric juice.

Case 4. A 38 year old woman presented with tetany. She had degree I osteomalacia. The serum Ca (5.1 mg.) was low. The serum inorganic P (3.6 mg.) and

TABLE II

Clinical Findings

Case	Weight Loss	Tetany	Bone Pain	Glossitis	Finger Clubbing	Osteomalacia Shown by X-Ray
1	+	0	0	+	0	0
2	+	0	+	0	0	+
3	+	0	0	0	0	0
4	0	+	0	0	0	0
5	+	+	0	0	+	0
6	0	0	+	0	0	+
7	+	+	0	0	0	0
8	+	+	0	+	+	0

the serum alkaline phosphatase (5 units) were normal. X-ray examination did not show decalcification of the bones. There was no evidence of renal disease.

Case 5. A 39 year old man presented with tetany. He had degree II osteomalacia. The serum Ca (6.7 mg.) was low, the serum inorganic P (2.9 mg.) was normal, and the serum alkaline phosphatase (25 units) was elevated. X-ray examination did not show decalcification of the bones. He had clubbing of the fingers. There was no evidence of renal disease.

Case 6. An 18 year old woman complained of knock-knees and severe pain in her hips and knees. She had degree IV osteomalacia. The serum Ca (8.5 mg.) was low, the serum inorganic P (3.3 mg.) was normal, and the serum alkaline phosphatase (45 units) was elevated. X-ray studies showed general decalcification of the skeleton and the typical picture of late rickets at the lower ends of the radii and upper ends of the tibiae. There was no evidence of renal disease.

Case 7. A 57 year old woman presented with severe megalocytic anemia and tetany. The red blood cell count was 0.9 million and the hemoglobin level 4.2 gm. A sternal puncture showed megaloblastic bone marrow. There was no free HCl in

TABLE III

Laboratory Data

Case	Anemia		Megaloblastic Bone Marrow	Elevated Prothrombin Time	Free Gastric HCl	Degree of Osteomalacia
	Megalocytic	Iron Deficiency				
1	+	0	+	+	+	0
2	0	0	−	+	−	4
3	0	+	0	0	+	0
4	0	0	0	0	+	1
5	0	0	0	0	+	2
6	0	0	−	0	+	4
7	+	0	+	+	0	1
8	0	0	−	+	+	1

−not done.

the gastric juice. The prothrombin time (35 seconds) was elevated. There was no glossitis and no neurologic disorder. She had degree I osteomalacia. The serum Ca (5.3 mg.) was low; the serum inorganic P (3.0 mg.) and the serum alkaline phosphatase (5 units) were normal. X-ray examination did not show decalcification of the bones. There was no evidence of renal disease.

Case 8. A 28 year old woman presented with tetany. She had degree I osteomalacia. The serum Ca (7.6 mg.) was low; the serum inorganic P (3.5 mg.) and the serum alkaline phosphatase (5 units) were normal. X-ray studies did not show decalcification of the bones. She had glossitis and clubbing of the fingers. The prothrombin time (44 seconds) was elevated. There was no evidence of renal disease.

The clinical features of these eight cases are all well recognized manifestations of idiopathic steatorrhea. However, a clinical diagnosis of this condition has traditionally rested on the occurrence of frequent, bulky, pale, unformed, offensive stools. In the present group of patients this distinctive sign was entirely absent. Consequently, fat balance studies were carried out to prove or exclude the presence of latent steatorrhea.

Fat Balance Studies

Observations were made over a 12 day balance period in six cases and over an eight day period in two. The daily diet contained 75 gm. of fat, 60 gm. of protein and 360 gm. of carbohydrate as calculated from food tables.[9] Seventy grams of this fat were contributed by three foods, milk, butter and eggs. The patients received this diet for three days before and then throughout the balance study. Carmine was used to mark the collection periods. The entire eight or 12 day stool was mixed with water to a uniform creamy consistency. Duplicate 150 ml. aliquots were dried to constant weight.* Fat was estimated gravimetrically after Soxhlet extraction with ethyl ether. Nitrogen was estimated by the macro-Kjeldahl method.

Table IV

Fat Balance Studies

Case	Balance Period Days	Stools Per Day	Fecal Fat		Fecal Nitrogen
			Gm. Per Day	% Intake	Gm. Per Day
1	12	1	22	30	2.1
2	12	1	14	19	1.4
3	12	1	12	16	0.9
4	8	1	13	17	0.9
5	12	1	16	21	1.1
6	12	1	8	11	0.7
7	8	1	11	15	2.1
8	12	1 or 2	27	36	1.8

The results are shown in table 4. Daily fecal fat ranged from 8 to 27 gm., representing 11 to 36 per cent of the intake. These data clearly indicate the presence of steatorrhea in every case. In normal adults on daily intakes of 50 to 200 gm. of fat, the fecal loss is always less than 10 per cent of the intake.[8, 10, 11, 12] The daily fecal nitrogen ranged from 0.7 to 2.1 gm. per day. These values are normal [10, 11, 12] and exclude pancreatic origin of the steatorrhea.

Treatment

All the patients responded well to measures commonly used in the treatment of idiopathic steatorrhea. Megalocytic anemia was corrected by oral folic acid in one case and by parenteral concentrated liver extract in the other. The one case of iron deficiency anemia was successfully treated with intravenous saccharated iron oxide. Iron by mouth was not used because we were investigating intravenous iron preparations at the time. Tetany and osteomalacia were readily controlled with calcium lactate and vitamin D by mouth. Prothrombin deficiency was corrected with vitamin K. A multi-

* In some instances an extra aliquot was acidified before drying. This did not affect the nitrogen values.

vitamin preparation was prescribed to relieve any deficiencies not clinically apparent. No dietary restrictions were imposed.

We have some data to indicate that steatorrhea persists despite treatment, but these studies are not complete.

Discussion

In 1923 Miller and Perkins [1] described five children with a "non-diarrhoeic type of coeliac disease." This resembled the classic type in all particulars except the stool, which was formed, well colored and not particularly offensive. Moreover, at no time had these children shown typical diarrhea alba. Our eight cases seem to represent the counterpart of this condition in adults.

It is well known that children with celiac disease and adults with idiopathic steatorrhea may experience long periods of apparent remission. During these periods diarrhea alba subsides and the stool appears normal on casual inspection. However, careful analysis will reveal persisting steatorrhea. Our cases do not appear to be examples of this, for at no time had they shown the characteristic stool.

The manifestations of idiopathic steatorrhea are protean. They include hypocalcemic tetany, osteomalacia, iron deficiency, megalocytic anemia and prothrombin deficiency. When no other cause is apparent, any of these should suggest idiopathic steatorrhea even though bowel symptoms have never been present.

Summary

Eight cases of latent steatorrhea in adults are described. Presenting conditions were tetany, osteomalacia, megalocytic anemia and iron deficiency. None had bowel symptoms to suggest the diagnosis. Steatorrhea was demonstrated by fat balance studies. Response to treatment was good in every case.

The protean manifestations of idiopathic steatorrhea are recalled. When no other cause is apparent, any of these should suggest the diagnosis even though bowel symptoms have never been present.

Latent steatorrhea has not received the attention it deserves, and it seems likely that the condition often goes unrecognized.

BIBLIOGRAPHY

1. Miller, R., and Perkins, H.: The non-diarrhoeic type of coeliac disease, Lancet **1**: 72, 1923.
2. Bennett, I., Hunter, D., and Vaughan, J. M.: Idiopathic steatorrhoea (Gee's disease): a nutritional disturbance associated with tetany, osteomalacia and anaemia, Quart. J. Med. **25**: 603, 1932.
3. Cooke, W. T., Elkes, J. J., Frazer, A. C., Parkes, J., Peeney, A. L. P., Sammons, H. G., and Thomas, G.: Anomalies of intestinal absorption of fat. 1. The determination and significance of faecal fat, Quart. J. Med. **39**: 141, 1946.

4. Israëls, M. C. G., and Sharp, J.: Idiopathic steatorrhoea (non-tropical sprue) with megaloblastic anaemia, Lancet **1**: 752, 1950.
5. Anderson, A.: Milkman's syndrome in idiopathic steatorrhoea complicated by refractory macrocytic anaemia, Lancet **2**: 897, 1950.
6. Strang, C.: The Looser-Milkman syndrome occurrence in a case of idiopathic steatorrhoea, Brit. J. Surg. **38**: 489, 1951.
7. Witts, L. J.: Pathogenesis of the megaloblastic anaemias, Lancet **2**: 367, 1951.
8. Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C., and Roos, A.: Osteomalacia and late rickets, Medicine **25**: 399, 1946.
9. Nutrition Division, Department of National Health and Welfare, Canada: Table of food values recommended for use in Canada, Ottawa, 1946.
10. Wollaeger, E. E., Comfort, M. W., Weir, J. F., and Osterberg, A. E.: The total solids, fat and nitrogen in the feces: I. A study of normal persons and of patients with duodenal ulcer on a test diet containing large amounts of fat, Gastroenterology **6**: 83, 1946.
11. Wollaeger, E. E., Comfort, M. W., and Osterberg, A. E.: Total solids, fat and nitrogen in the feces: III. A study of normal persons taking a test diet containing a moderate amount of fat; comparison with results obtained with normal persons taking a test diet containing a large amount of fat, Gastroenterology **9**: 272, 1947.
12. Fourman, L. P. R., Higgins, G., Quelch, P., O'Brien, J. R. P., and Witts, L. J.: The investigation and diagnosis of steatorrhoea, Clin. Sc. **7**: 121, 1948.

SYSTEMIC LUPUS ERYTHEMATOSUS PRECEDED BY FALSE-POSITIVE SEROLOGIC TESTS FOR SYPHILIS: PRESENTATION OF FIVE CASES *

By JOHN R. HASERICK, M.D., *Cleveland, Ohio,* and ROLAND LONG, 1st Lieut., M.C., *Fort Jackson, South Carolina*

BIOLOGIC false-positive serologic tests for syphilis have frequently been observed in patients with all types of lupus erythematosus.[1-6] The time relationship between the development of these serologic alterations and the onset of clinical manifestations of lupus erythematosus is unknown. We have been unable to find reports of cases in which false-positive tests for syphilis were observed *prior* to the clinical manifestations of lupus erythematosus (L. E.).

The purpose of this communication is to report five cases in which false-positive serologic tests for syphilis were observed before the onset of clinical manifestations of systemic (positive plasma L. E. test [7, 11]) lupus erythematosus.

In a series of 29 patients with systemic lupus erythematosus observed at the Cleveland Clinic during the past two years, seven have had positive serologic tests for syphilis. In one, a history of infectious syphilitic lesions was obtained. Another, a 13 year old girl, was found to have positive serologic tests for syphilis only after the onset of classic acute disseminated lupus erythematosus. In the remaining cases, positive serologic tests for syphilis occurred one to seven years *before* the first symptoms of systemic lupus erythematosus. These cases are presented in the following case reports.

CASE REPORTS

Case 1. A 24 year old white unmarried woman was first seen at the Cleveland Clinic on December 24, 1946, with a chief complaint of painful swollen joints and "rheumatic fever" of one month's duration. Past history revealed positive serologic tests for syphilis in 1943, discovered when the patient attempted to donate blood. The cerebrospinal fluid was normal. Sexual exposure was denied. There was no history of lesions resembling those of infectious syphilis. Serologic studies performed on members of her family were negative. At another hospital a dermatologic consultant diagnosed the serologic tests as false-positive. Her family physician treated her with arsenical and bismuth medication for four months, followed by 3 million units of penicillin.

* Presented at Midwest Regional Meeting of American College of Physicians in Columbus, Ohio, on October 13, 1951. Received for publication October 17, 1951.

From the Cleveland Clinic and The Frank E. Bunts Educational Institute, Department of Dermatology, Earl W. Netherton, M.D., Chief.

This investigation was made possible in part by a research grant from the National Institutes of Health, United States Public Health Service.

Physical Examination: The initial examination revealed the temperature to be 99.4° F., the pulse 100, and the blood pressure 120/80 mm. of Hg. Physical examination was negative except for a discrete node in the left axilla and a spindle-shaped swelling of all finger joints.

Laboratory: The hemoglobin was 12.5 gm. per 100 c.c. and the leukocyte count 7,650. The sedimentation rate was 1.1 mm./minute (normal, .45). Two plus albuminuria was noted. The Wassermann reaction was negative and the Kahn 4 plus.

Course: In 1946 the patient was treated symptomatically for rheumatoid arthritis. On February 10, 1947, elevated, pruritic, well demarcated plaques were noted on the forearms and backs of the hands. The dermatologic consultant diagnosed the condition as toxic erythema, but suggested lupus erythematosus as a possibility. Facial lesions developed in June, 1948, after exposure to the sun. At this time the Wassermann reaction was 4 plus and the Kahn 1 plus. The plasma proteins on June 8, 1948, by the Tiselius method revealed a low albumin (41 per cent), increased alpha (12.3 per cent) and gamma (23 per cent) globulin. General malaise, weakness and a susceptibility to infections were noted. The albuminuria increased to 8.9 gm. per liter, and 14 million erythrocytes were noted in the Addis count. A bone marrow examination by the Hargraves [10] technic on February 7, 1949, revealed no evidence of the lupus erythematosus phenomenon. The plasma L. E. test [7, 11] was strongly positive on May 18, 1949. The course was progressively downward, and the patient died at another hospital. The final pathologic diagnoses after postmortem examination were reported as follows: "(1) Widespread arteritis and arteriolitis; (2) lupus erythematosus disseminatus, and (3) subacute interstitial nephritis, consistent with lupus erythematosus."

Summary: False-positive serologic tests for syphilis first noted in 1943, three years before the first sign of lupus erythematosus. Positive plasma L. E. test in 1949. Autopsy later confirmed diagnosis of systemic lupus erythematosus.

Case 2. A 34 year old white married woman was admitted to the Cleveland Clinic Hospital on November 8, 1948, acutely ill with lupus erythematosus. The present illness had begun one year prior to admission with the onset of "rheumatism." The knees, feet and hands were most severely involved. Four months prior to admission she developed fever, ulcerations of the mouth, and erythema of the face and upper arms following exposure to the sun. This was followed by weakness, anorexia and nausea. There was no response to 12 daily injections of penicillin.

Past History: Positive serologic tests for syphilis were discovered in 1945 when the patient attempted to donate blood. There was no history of primary or secondary syphilis. Serologic studies of her husband and members of her own family were negative. The tests were inconstant, and usually weakly positive to negative. From 1945 to 1947 the patient received approximately 17 injections of Mapharsen and 20 injections of bismuth. No penicillin was administered until November, 1948.

Physical Examination: An extensive maculopapular eruption was noted over the face and to a lesser extent over the arms. Generalized lymphadenopathy was present. The heart and lungs were normal. There was tenderness of the small joints but no gross deformity. The temperature varied from 100.2° F. on admission to 105° F. several days later. The pulse rate was 134. The blood pressure was 104/84 mm. of Hg.

Laboratory: Routine laboratory studies on admission revealed the hemoglobin to be 9 gm. per cent, leukocyte count, 3,150, and the sedimentation rate increased to 1.75 mm./min. (normal, .45). The Wassermann and Kahn reactions were negative. Two plus albuminuria and microscopic hematuria were noted. Concentrated bone marrow preparations revealed rosettes of leukocytes and L. E. cells. The plasma L. E. test was positive. The plasma proteins by the Tiselius method were as follows: albumin, 42.9 per cent (normal range, 60.1 to 67.2 per cent); alpha globulin, 4.9 per

cent (normal range, 6.0 to 8.7 per cent); beta globulin, 18.2 per cent (normal range, 11.0 to 15.9 per cent); gamma globulin, 24.4 per cent (normal range, 8.6 to 14.8 per cent); and fibrinogen, 9.6 per cent (normal range, 2.8 to 7.2 per cent).

Course: After a prolonged, stormy course during which the patient was treated with blood transfusions, liver extract, testosterone and aureomycin, she gradually improved and was discharged on February 7, 1949. On January 17, 1950, she had shown a remarkable improvement. The eruption and the joint pains had disappeared, and the plasma L. E. test was negative.

Summary: History of persistently positive, though weak, serologic tests for syphilis three years before onset of clinical lupus erythematosus resulted in treatment for latent syphilis. Psychic trauma very great. Penicillin employed after onset of symptoms of lupus erythematosus.

Case 3. A 25 year old unmarried woman was first seen at the Cleveland Clinic on July 6, 1943, because of a history of positive serologic tests for syphilis since a premarital examination in 1941. There were no presenting complaints. There was no history of primary or secondary lesions of syphilis. She denied any sexual exposure. Marriage was postponed because of the positive serologic studies and the patient became a recluse. From April, 1942, until January, 1943, she received 14 injections of bismuth and 27 injections of neoarsphenamine. Four subsequent Wassermann tests were reported as negative.

Physical examination was normal. There were no stigmata of congenital syphilis. The introitus would admit one finger. The routine laboratory studies were normal except for a 2 plus Kahn reaction. The Wassermann was negative. Spinal fluid examination was normal. Special blood sent to Dr. Kline, of the Mt. Sinai Hospital of Cleveland, was reported as a positive test for syphilis.

Course: From August, 1943, until December, 1944, the patient received 30 injections of Mapharsen and 40 injections of bismuth. Wassermann and Kahn reactions were negative at completion of treatment. General health remained good until April 8, 1946, when the patient developed a persistent cough. Physical examination was normal. A roentgenogram of the chest was interpreted as chronic bronchitis. On July 19, 1947, the Wassermann reaction was 2 plus and the Kahn reaction 2 plus. They were both 4 plus on August 11, 1948. A persistently low hemoglobin was noted, which did not respond to iron therapy. On December 1, 1948, she noted the onset of weakness, fever and abdominal cramps in association with the onset of a menstrual period. The Wassermann and Kahn reactions were 4 plus; the Kahn quantitated at 80 units. The patient was started on a course of penicillin. After receiving 2,400,000 units of penicillin, this was discontinued because of bilateral pitting ankle edema. She became progressively weaker and was admitted to the Cleveland Clinic Hospital on May 10, 1949. The general examination revealed the blood pressure to be 144/94 mm. of Hg. The hemoglobin was 9.5 gm. per 100 c.c. The leukocyte count was 3,800, with 65 per cent neutrophils, 21 per cent lymphocytes, 4 per cent eosinophils and 10 per cent monocytes. The icterus index was 4, and the platelets were normal. The serum Tiselius electrophoretic pattern was as follows: albumin, 39.4 per cent; alpha globulin, 28.4 per cent (normal, 6. to 8.7 per cent); beta globulin, 16.5 per cent (normal, 11. to 15 per cent); second gamma globulin, 15.7 per cent (normal, 8.6 to 14.8 per cent). The urinalysis revealed a specific gravity of 1.012, 3 plus albuminuria, and microscopic hematuria. The plasma L. E. test was strongly positive. The patient's subsequent progress was stormy, with episodes of high fever. She was discharged from the hospital on June 15, 1949, and died at her home July 15, 1949, after the development of pericarditis and pleural effusion.

Summary: False-positive serologic tests for syphilis first noted in premarital examination eight years before recognizable signs and symptoms of systemic lupus erythematosus. Diagnosis of syphilis resulted in severe reactive depression. Wasser-

mann and Kahn titers increased with onset of clinical manifestations of lupus erythematosus. Onset of final illness coincidental with administration of penicillin.

Case 4. A 41 year old married woman was first seen at the Cleveland Clinic on May 2, 1947, complaining of weakness and pains in the arms and legs. The onset of her trouble had followed an attack of influenza in December, 1946. The shoulders, elbows, knees and ankles were the joints most affected. Swelling of the right hand was noted.

Past History: Positive serologic tests for syphilis were first found in 1945. There was no history of primary or secondary syphilitic lesions. Treatment had consisted of an unknown number of weekly intramuscular injections. Penicillin was never administered.

Physical examination revealed the temperature to be 99.2° F. There were erythema and tenderness of the knees but no other findings of note.

Laboratory: The hemoglobin was 12 gm. per 100 c.c., and the leukocytes numbered 1,900. The sedimentation rate was increased to 1.5 mm. (normal, .45). The fasting blood sugar and uric acid determinations were normal. The specific gravity of the urine was 1.017. Two plus albuminuria was found. The urinary sediment was normal. The Wassermann reaction was negative. The Kahn was 2 plus. The examination of the spinal fluid was normal.

Course: Diagnoses of osteoarthritis and latent syphilis were made. The patient responded quite well to typhoid vaccine and salicylate therapy. She entered into a partial remission until March, 1950, at which time she became acutely ill with high fever, prostration, polyserositis and frequent epileptic seizures. On admission to another hospital she appeared moribund. The plasma L. E. test was strongly positive. Her hemoglobin had dropped to 3 gm., and did not respond to transfusions. A striking improvement was noted following the use of cortisone and ACTH. Her improvement was steady, and she was placed upon maintenance steroid therapy. The epileptic attacks ceased. Several months later she developed a sudden air hunger and died. Permission for post mortem was not granted her attending physician.

Summary: Probable false-positive serologic tests for syphilis occurring almost two years before early symptoms consistent with lupus erythematosus, and five years before entering the acute phase of this disease.

Case 5. A 24 year old married woman was admitted to the Cleveland Clinic Hospital on September 6, 1950, complaining of weakness, fever and joint stiffness. In 1946 she first noted fleeting arthralgias and stiffness of the fingers. At times she felt normal. Two years later pleurisy of the right side developed which was associated with an increase in weakness and malaise. A "butterfly" erythema over the bridge of the nose was first noted in the fall of 1949. She was frequently bedridden. In March, 1950, the temperature increased to 103° F. in the afternoons. Stiffness and swelling of the fingers increased. Anorexia and vomiting occurred frequently during the 10 days before admission.

Physical examination on admission revealed the temperature to be 101° F. and the pulse rate 100. There was a slight erythema over the bridge of the nose and on the cheeks. The blood pressure was 95/50 mm. of Hg. She appeared subacutely ill. The inguinal and axillary lymph nodes were palpable. The rest of the examination was essentially negative.

Past History: A premarital examination revealed positive serologic tests for syphilis in 1946, before the onset of symptoms. She denied sexual exposure, or primary or secondary lesions of syphilis. Treatment consisted of a course of penicillin in 1946, and bismuth and arsenic in 1948.

Laboratory: The hemoglobin was 10.5 gm. per 100 c.c. The leukocyte count varied from 4,050 to 7,000. The differential count was normal. The urinalysis was

normal. The sedimentation rate was 1.65 (normal, .45). The plasma L. E. test was positive on repeated occasions. The Wassermann reaction was negative. The Kahn was 4 plus, quantitatively 40 units. The plasma proteins by the Tiselius method were as follows: albumin, 43 per cent (normal, 60.1 to 67.2 per cent); alpha globulin, 4.9 per cent (normal, 6. to 8.7 per cent); beta globulin, 18.6 per cent (normal, 11 to 15.9 per cent); gamma globulin, 25.6 per cent (normal, 8.6 to 14.8 per cent); and the fibrinogen, 7.9 per cent (normal, 2.8 to 7.2 per cent). Blood samples sent to Dr. Kline, of the Mt. Sinai Hospital, Cleveland, were reported as "probable false-positive serologic tests for syphilis."

Course: The patient made a prompt response on steroid therapy and is doing well on a maintenance regimen. The Kahn reaction and the plasma L. E. test remain positive.

Summary: False-positive serologic tests for syphilis occurring shortly before early symptoms of lupus erythematosus, and four years before severe attack of the disease resulted in unnecessary treatment for nonexistent syphilis.

Comment

The literature contains many references to the association between biologic false-positive reactions for syphilis and lupus erythematosus.[1-6] The frequency of this association has varied in accordance with the type of lupus erythematosus and the battery of serologic tests employed. Montgomery and McCreight [5] found positive serologic tests for syphilis in 44 per cent of their cases with acute disseminated lupus erythematosus, 25 per cent of the subacute, and 17 per cent of the chronic. The same authors, in an earlier series, found the proportion to be 17, 11 and 6 per cent, respectively. The difference between the two groups was attributed to the fact that in the earlier series only one or two tests were done, whereas in the more recent group four serologic tests were performed.

Rein and Kostant [6] performed a battery of six serologic tests for syphilis on the serum of 176 patients with lupus erythematosus. Thirty-five per cent gave positive reactions to one or more of the tests in the battery. They stated that the "serologic phenomena may be the first and only sign of lupus erythematosus and may warn of impending clinical activity," but did not enlarge on this observation.

Coburn and Moore [4] found 11 of 30 cases of disseminated lupus erythematosus had positive Wassermann or anti-complementary reactions. Hypergammaglobulinemia was a constant characteristic of their cases. They separated the globulin fractions electrophoretically and tested the individual fractions for activity with the Wassermann and Kahn antigens. The antibody was found to be mostly in the gamma fraction and partly in the beta $_2$ fraction.

More specific plasma alterations were discovered through investigations into the "L. E. factor," which is responsible for the entire lupus erythematosus phenomenon noted first in the patient's own bone marrow.[10] After the discovery that the L. E. phenomenon could be artificially induced in normal human or even dog marrow by simple admixture with L. E. plasma,[11]

fractionation studies revealed that the L. E. factor was contained within the gamma globulin portion of systemic lupus erythematosus plasma.[8] Immunologic studies in rabbits revealed the L. E. factor to be antigenically specific from normal gamma globulin.[8]

Further experience with the plasma L. E. test since it was first employed at the Cleveland Clinic in February, 1949, has indicated that it is an extremely valuable and accurate indicator of systemic lupus erythematosus. In several cases the plasma L. E. test was positive when the clinical course was mild and atypical, and the diagnosis of systemic lupus erythematosus was considered to be remote indeed. Three such patients subsequently died with explosive overwhelming lupus erythematosus.[13] Hargraves,[14] using his L. E. test based upon the patient's own marrow, and Soffer,[15] whose laboratory employs both L. E. tests, expressed confidence that these procedures are reliable in detecting atypical cases.

The plasma L. E. test and the false-positive serologic tests for syphilis wax and wane with the clinical course of the disease. With control of the clinical manifestations of lupus erythematosus with steroids, the plasma L. E. test not infrequently reverts to negative, and the serologic tests for syphilis show low titers. It remains to be seen whether the plasma L. E. test can also be positive when the patient apparently shows no manifestations of the disease.

It is clear that a more widespread employment of the plasma L. E. test is indicated, particularly when patients suffering with atypical forms of glomerulonephritis, rheumatic fever and rheumatoid arthritis also have unexplained serologic tests for syphilis.

The pathogenesis of lupus erythematosus is unknown. The present study suggests that false-positive serologic tests for syphilis may in some cases be the first indication of lupus erythematosus, years before the outbreak of clinical symptoms. A "diathesis" for lupus erythematosus is thus suggested. This conception is supported in the previously reported [16] cases of "epilepsy" in lupus erythematosus, in which convulsive seizures were noted in two patients for years prior to the onset of the symptoms of lupus erythematosus. A third case has been seen since: the patient first noted convulsive attacks at the age of five years and "rheumatoid arthritis" at 15 years; a positive plasma L. E. test was found at 17 years.

Summary

1. False-positive serologic tests for syphilis are reported in five patients with systemic lupus erythematosus.

2. In each instance the false-positive reactions occurred for from one to seven years *before* the onset of clinical manifestations of lupus erythematosus.

3. These data suggest that patients with positive serologic tests for syphilis and atypical rheumatoid arthritis, rheumatic fever or glomerulonephritis may actually be latent cases of systemic lupus erythematosus.

4. The plasma L. E. test is recommended as a diagnostic procedure in such cases.

5. The existence of a predisposition for lupus erythematosus is suggested.

BIBLIOGRAPHY

1. White, C. J.: The problem of positive serologic tests for syphilis in lupus erythematosus, Am. J. Syph., Gonor. and Ven. Dis. **31**: 235, 1947.
2. Keil, H.: Dermatomyositis and systemic lupus erythematosus, Arch. Int. Med. **66**: 339, 1940.
3. Gennerich, cited by Keil.[2]
4. Coburn, A. F., and Moore, D. H.: The plasma proteins in disseminated lupus erythematosus, Bull. Johns Hopkins Hosp. **73**: 196 (Sept.) 1943.
5. Montgomery, H., and McCreight, W. G.: Disseminate lupus erythematosus, Arch. Dermat. and Syph. **60**: 356 (Sept.) 1949.
6. Rein, C. R., and Kostant, G. H.: Lupus erythematosus: serologic and chemical aspects, Arch. Dermat. and Syph. **61**: 898 (June) 1950.
7. Haserick, J. R., and Bortz, D. W.: New diagnostic test for acute disseminated lupus erythematosus, Cleveland Clin. Quart. **16**: 158, 1949.
8. Haserick, J. R., Lewis, L. A., and Bortz, D. W.: Blood factor in acute disseminated lupus erythematosus. I. Determination of gamma globulin as specific protein fraction, Am. J. M. Sc. **219**: 660, 1950.
9. Haserick, J. R., and Lewis, L. A.: Blood factor in acute disseminated lupus erythematosus. II. Induction of specific antibodies against L. E. factor, Blood **5**: 718, 1950.
10. Hargraves, M. M., Richmond, H., and Morton, R.: Presentation of two bone marrow elements: "tart cell and L. E. cell," Proc. Staff Meet., Mayo Clin. **23**: 25, 1948.
11. Haserick, J. R., and Bortz, D. W.: Normal bone marrow inclusion phenomenon induced by lupus erythematosus plasma, J. Invest. Dermat. **13**: 47, 1949.
12. Moore, J. E.: The modern treatment of syphilis, 2nd Ed., 1944, Chas. C Thomas, Springfield, Illinois.
13. Haserick, J. R.: Plasma L. E. test in systemic lupus erythematosus: study of 23 patients with positive tests, J. A. M. A. **146**: 16 (May 5) 1951.
14. Hargraves, M. M.: Symposium on lupus erythematosus, Univ. of Minnesota, Minneapolis, April 5-6, 1951.
15. Soffer, L. J.: Symposium on lupus erythematosus, Univ. of Minnesota, Minneapolis, April 5-6, 1951.
16. Russell, P., Haserick, J. R., and Zucker, E. M.: Epilepsy in systemic lupus erythematosus, Arch. Int. Med. **88**: 78-92 (July) 1951.

ALCOHOLIC NEURITIS *

By WARREN F. GORMAN, *New York, N. Y.*

THE purpose of this article is to describe alcoholic neuritis briefly from a clinical, physiologic and therapeutic point of view.

Alcoholic neuritis is a term that has been used to describe the neuropathy which appears in alcoholics. Neuritis, or inflammation of a nerve, is not present in this condition; hence the term neuropathy, connoting disease of a nerve, is preferable.[49, 23] Further, the neuropathy is not directly due to alcohol but is caused by the nutritional deficiencies which may accompany alcoholism.[16, 19] An alcoholic may be defined as a person who is disabled or diseased by the excessive use of alcohol. Alcoholics are disordered in their social and interpersonal relations, many exhibiting the signs of a neurosis or psychosis.[46] Concomitantly, there may be disorders in many organ systems, particularly the gastrointestinal,[3] the endocrine [36, 38] and the central nervous systems. Alcoholism is thus a disease of the patient as a whole, producing many widespread signs and symptoms of which neuropathy is but one local feature. Through customary usage, neuropathy applies to disorders of the peripheral nerves, while encephalopathy and myelopathy pertain to brain and spinal cord disease, respectively. A group of 25 alcoholics with encephaloneuropathy furnished the principal material for this communication; neuropsychiatric study of these individuals has been reported elsewhere.[19]

Clinically, neuropathy appears in some, but not all, alcoholics who do not eat when they drink, or whose diet is in some way inadequate.[48] While young people may demonstrate this condition, it is more usual in persons of mature years. Males and females are equally affected. There is no definite relationship between the incidence of neuropathy and the type of alcoholic beverage which is consumed. Drinkers of beer, wine and distilled liquor all may show alcoholic neuropathy. Some alcoholics prefer beers and wines because of their lower cost and greater dilution, but most will drink distilled liquor when the opportunity presents.

Other drugs than alcohol are used by alcoholics. Methyl alcohol may be ingested deliberately or unknowingly. In sufficient amounts, this substance announces its presence by such signs as optic neuritis, convulsions and peripheral neuropathy. However, small amounts of alcohol decrease the toxicity of methyl alcohol, possibly by inhibition of the breakdown of methyl alcohol to formic acid.[1, 39] Tricresyl phosphate, or Jamaica ginger jake, can produce a severe myeloneuropathy.[22] Bromides can be self-prescribed and may cause a typical organic psychosis.[21] Barbiturates are frequently used by alcoholics, some being addicted to the short-acting barbi-

* Received for publication August 17, 1951.

turates. Withdrawal of barbiturates from the barbiturate addict who is also an alcoholic may readily produce convulsive seizures.[33] An alcoholic with kidney or liver disease, however, may become heavily narcotized, or stuporous, with a relatively small dose of barbiturate. Nystagmus appears in both barbiturate intoxication and alcoholic encephalopathy.[5]

Infections may predispose the alcoholic toward neuropathy. Alcoholics are subject to trauma, especially head injuries, and post-traumatic epilepsy is not uncommon.[20] Local trauma to an extremity may precipitate or aggravate the neuropathy in a limb or a single nerve, as in "Sunday morning palsy."

Clinical Findings

The patient often complains of spontaneous pains in the calves of the legs, and of a tremor. There may be "nervousness," consisting either of the concatenation of tension and anxiety, or a tremor of the extremities, or of both psychologic and somatic manifestations. The tremor is present at rest and increases with activity. It tends to be intermediate in rate between the tremor of Parkinsonism (3 to 8 per second) and that of the anxiety state, or in hyperthyroidism (about 15 to 30 per second). Similar tremors are present about the mouth, tongue and face. Generalized motor weakness is the rule and, in addition, there is weakness of the extremities, more pronounced in the legs. Foot drop is a not uncommon finding, but wrist drop is not often seen. The ankle jerk is lost early in the course of the disease and does not return until late in the phase of recovery. The knee jerk, less often absent, disappears later and reappears sooner.[9, 49] It should be emphasized that it can be difficult both to elicit and to evaluate reflexes in a tremulous alcoholic; the extremities should be placed in a position of semiflexion at all joints and the patient's comfort assured during examination.

Vasomotor and trophic changes appear as frequently as in other forms of neuropathy. The skin is often dry and scaling in appearance, but there may also be excessive sweating over the dorsum of the foot. There may be a grayish discoloration of the skin in the distal portions of the extremities. Although hypertrichosis and sometimes hypotrichosis appear in other forms of neuropathy,[44] alcoholics of both sexes, both with and without neuropathy, usually show little hair on the extremities.[36] Alcoholic neuropathy is uncommon in patients with peripheral vascular disease.

Sensation is significantly disturbed in alcoholic neuropathy. There is tenderness on compressing the calves in most instances. Palpation of readily accessible nerve trunks—the ulnar, peroneal and sciatic—does not elicit marked tenderness but may produce a tingling sensation in the peripheral cutaneous distribution of these nerves. Stroking the soles of the feet may result in an "electric" feeling, or in a delayed and excessively painful response. This latter phenomenon is a perversion of sensation which is described as delayed hyperpathia.[19] A typical example is seen when one

gently strokes the sole of the foot with a pin, as in the technic used to evoke the Babinski reflex; about one second after the stroke is completed, the patient describes a sharp pain radiating up the leg for an additional two or three seconds. At times, delayed and excessive calf tenderness is found.[4, 6]

The distal portions of the extremities (glove and stocking areas) show diminution or sometimes exaggeration of the sensation of pin-prick. It is interesting that some patients with decreased sensitivity to a single pin-prick on the sole will show delayed hyperpathia arising from the same area. Vibration sense is usually lost in the distal portions of the legs. The patient cannot perceive vibration of the 128-vibrations-per-second tuning-fork below the knee; with higher pitched tuning forks (256 vibrations per second), this loss is more apparent, and hyp-pallesthesia appears in the fingers as well. At times the vibration is perceived as a painful tingling. Light touch with the examiner's finger or with a wisp of cotton is not so well perceived over the glove and stocking areas as it is in normal individuals. Position sense, as tested by the ability to perceive whether a digit has been moved up or down, is not impaired.

Complications

Complications of alcoholism are many.[26] Alcoholics may show mental changes compatible with the diagnosis of a neurosis or psychosis. In the Korsakoff syndrome, there is both a confabulatory psychosis (the Korsakoff psychosis) and peripheral neuropathy.[30] Delirium tremens, Wernicke's syndrome and Korsakoff's syndrome are clinical instances of severe organic disturbances in the central nervous system of alcoholics. There is a close relationship between these three syndromes, both clinically and pathologically; they are, in fact, progressive phases in the course of encephaloneuropathy which appears in chronic alcoholics.[19] Acute alcoholic hallucinosis is characterized by terrifying auditory hallucinations in the presence of an apparently clear sensorium, and it requires careful differentiation from schizophrenia. Myelopathy appeared in one-fifth of a group of patients with alcoholic neuropathy.[17] Psychiatric and physiologic study of alcoholics has yielded a large body of literature, and many excellent summaries have been published.[10, 48, 27]

Etiology

The etiology of alcoholic neuropathy is apparently nutritional. Vitamin deficiencies,[28, 2] the effect of antivitamins and vitamin imbalance [11] have all been implicated as a cause of alcoholic neuropathy. It has been shown that individuals may take massive amounts of alcoholic beverages and not develop neuropathy, provided their diet is adequate.[41] The symptomatology and pathologic findings in the peripheral nerves are essentially the same in malnutrition, in cases of pellagra and in alcoholic neuropathy.[2] Alcohol itself does not cause neuropathy. Multiple deficiencies of nutrition, including

the vitamins of the B group, are usually found. Thiamine is almost always deficient in alcoholics with neuropathy.[28] It has been generally believed that the demand for thiamine is increased by the consumption of alcohol. However, this theory has been controverted by recent work in which an isocaloric substitution of alcohol for carbohydrate was done, but the thiamine excretion of the experimental subjects actually increased.[11]

The vitamin content of alcoholic beverages is low, although beer has the caloric value of milk, and wine the caloric value of soft drinks. Distilled liquors and wines have little to no water-soluble vitamin content. The vitamin content of beer is also minute, as the vitamins of the yeast used in its manufacture do not appear in the potable product.

From a clinical standpoint, however, it should be emphasized that malnutrition is not uniformly associated with neuropathy. Only one-fourth of a large group of malnourished alcoholics with encephalopathy evinced the signs of peripheral neuropathy. Further, among a group of prisoners of war who were malnourished but were not alcoholic, neuropathy (as evidenced by calf tenderness and absent ankle jerks)[7] appeared in only approximately one-fourth of the total number.

To add further to the complexity of the etiologic picture, compression of an extremity by means of a sphygmomanometer cuff causes the gradual appearance of symptoms similar to those of alcoholic neuropathy.[47] The larger nerve fibers are affected first in both conditions.[14, 15] The smallest nerve fibers, which transmit impulses slowly and are said to carry painful sensation such as "second pain," are affected last, perhaps accounting for the delayed hyperpathia which has been described.[47] However, painful sensations are carried by fibers of small, medium and large diameter.[14, 12]

When a normal individual is subjected both to compression by a sphygmomanometer cuff to an extremity and to a noxious stimulus to the hand or foot, burning pain is readily produced and lasts for five seconds or more after the stimulus stops.[8] Under similar circumstances, the interruption of alpha rhythm in the electroencephalogram is delayed by about one second.[18] However, after anesthetizing the ulnar nerve and producing a third degree burn in the area supplied by this nerve, burning pain persisted for 24 hours.[8]

The toxicity of vitamins A, D and E and para-aminobenzoic acid has been well documented.[11] Antivitamin and vitamin antagonists are also well known. There is, for example, an anti-niacin compound in corn. Folic acid (pteroylglutamic acid) (in the absence of B_{12}) has caused an explosive increase of toxic signs referable to the spinal cord and peripheral nerves of patients with pernicious anemia.[25] Folic acid antagonists, e.g., aminopterin, are well known. The relationship between folic acid and its antagonists has not been conclusively settled, nor do we know the relationship between these vitamin systems and the neuropathies which are apparently due to nutritional disorders.

Vitamin B_{12}, on the other hand, not only produces a marked remission in pernicious anemia but also is of marked benefit in the neurologic manifestations of this condition. Vitamin B_{12} is now available in combination with hog duodenal mucosa, which renders it effective by oral administration in amounts as low as 5 micrograms daily.[24, 7, 27] Recognizing that the neuropathies in pernicious anemia and in alcoholics are only distantly related, a therapeutic trial was made with vitamin B_{12} in alcoholic neuropathy. Two patients with early alcoholic neuropathy were treated with an orally effective vitamin B_{12} compound. The results of this treatment, although incomplete at present, are encouraging.

Treatment and Prognosis

Treatment of alcoholic neuropathy consists of vitamin replacement, care of the medical and surgical complications of the alcoholic condition, and physiotherapy. The diet must be adequate and is usually supplemented by the addition of crude polyvitamin concentrates. Vitamin B_{12}, now under trial, has shown definite promise. Crude liver concentrate, 2 c.c. twice weekly by intramuscular injection, has been used with satisfactory results. Physiotherapeutic procedures, particularly gentle passive exercise and whirlpool baths, are of benefit to these patients with foot drop or marked weakness.

The prognosis for mild cases of alcoholic neuropathy is good.[19, 24] The more severe cases persist for many months and may never recover. In milder treated cases, the patients are usually able to walk in three or four days, the knee jerks return in two weeks, vibration sense and the ankle jerks return in three weeks, and calf tenderness disappears in less than a month. Untreated mild cases improve very little. In the more severe cases, encephalopathy, myelopathy and liver disease may preclude general recovery. In cases of severe Korsakoff's syndrome, the psychosis and peripheral neuropathy often persist for years.

Since 1943, the incidence of severe alcoholic neuropathy has been considerably less than in previous years. One factor contributing to this may be that bread, a food sufficiently cheap and palatable to be eaten in at least small quantities by severe alcoholics, has been enriched with thiamine and other water soluble vitamins since 1943.

Summary

Alcoholic neuritis or neuropathy is a relatively uncommon disorder among the many somatic and psychiatric disturbances of alcoholics. In alcoholic neuropathy involving the peripheral nerves, there are general weakness and increased weakness of the distal portions of the extremities. Foot drop and wrist drop may be seen. The ankle jerk is usually absent and the knee jerk less often absent. During recovery, the ankle jerk returns

later than the knee jerk. Moderately fine tremors are present in the extremities and face. Vasomotor and trophic changes are noted in the extremities. Sensory complaints include spontaneous pains in the calves. There is tenderness of the calf and sole. The glove and stocking areas show diminution of vibration sense and of light touch. There may be diminished or increased sensitivity to pin-prick in these areas. Perversions of sensation are noted, including perception of vibration as painful tingling, and delayed hyperpathia. Delayed hyperpathia is elicited by gently stroking the sole with a pin, after which there is a delay of one second, followed by a sharp tingling pain which radiates up the foot and leg for two to three seconds. Alcoholic neuropathy is apparently caused by vitamin deficiencies and malnutrition; the rôle of antivitamins is not yet clear. Alcohol does not cause alcoholic neuropathy. The few excised nerves which have been examined pathologically show fatty degeneration and fragmentation of myelin. Treatment consists of adequate diet, crude polyvitamin supplements, liver extract injections and physiotherapy. The prognosis is good only for mild cases. Alcoholic neuropathy may be accompanied by myelopathy and encephalopathy, as seen in delirium tremens, and in Wernicke's and Korsakoff's syndromes; by craniocerebral trauma, convulsions and by barbiturate and bromide addiction, as well as gastrointestinal, endocrine and psychiatric disorders.

BIBLIOGRAPHY

1. Agner, K., Hook, O., and Von Porat, B.: Treatment of methyl alcohol poisoning with ethanol, Quart. J. Stud. on Alcohol **9**: 515, 1949.
2. Aring, C. D., Bean, W. B., Roseman, E., Rosenbaum, M., and Spies, T. D.: The peripheral nerves in cases of nutritional deficiency, Arch. Neurol. and Psychiat. **45**: 772, 1941.
3. Beazeale, J. M., and Ivy, A. C.: Influence of alcohol on digestive tract, Quart. J. Stud. on Alcohol **1**: 45, 1940.
4. Bender, L.: Myelopathia alcoholia, Arch. Neurol. and Psychiat. **31**: 310, 1934.
5. Bender, M. B., and Gorman, W. F.: Vertical nystagmus and oscillopsia, Am. J. Ophth. **32**: 967, 1949.
6. Bender, L., and Schilder, P.: Encephalopathia alcoholia, Arch. Neurol. and Psychiat. **29**: 990, 1933.
7. Bethell, F. H., Swendseid, M. E., Myers, M. C., Neligh, R. B., and Richards, H. G.: Hog duodenal mucosa potentiating B_{12} oral therapy, Univ. Hosp. Bull., Ann Arbor, Michigan **15**: 49, 1949.
8. Bigelow, N., Harrison, J., Goodell, H., and Wolff, H. G.: Studies on pain with reference to peripheral neuritis, J. Clin. Investigation **24**: 503, 1945.
9. Bowman, K. M.: *in* The practitioner's library of medicine and surgery, Vol. IX, 1936, D. Appleton Century Co., New York, p. 365.
10. Bowman, K. M., and Jellinek, E. M.: Alcoholic mental disorders, Quart. J. Stud. on Alcohol **2**: 312, 1941.
11. Culver, P. J.: Vitamin supplementation in health and disease, New England J. Med. **241**: 970, 1051, 1950.
12. Denny-Brown, D., and Brenner, C.: Lesions in peripheral nerves resulting from compression by a spring clip, Arch. Neurol. and Psychiat. **52**: 1, 1944.
13. Denny-Brown, D., and Brenner, C.: Paralysis of nerve induced by direct pressure and by tourniquet, Arch. Neurol. and Psychiat. **51**: 1, 1944.

14. Gasser, H.: Pain producing impulses in peripheral nerves, Proc. A. Research Nerv. and Ment. Dis. **23**: 44, 1943.
15. Gasser, H.: Control of excitation in the nervous system, Harvey Lectures, 1937, Williams & Wilkins Co., Baltimore, p. 169.
16. Gildea, E. F.: *in* The practitioner's library of medicine and surgery, vol. IX, 1936, D. Appleton Century & Co., New York, p. 424.
17. Gildea, E. F., Kattwinkel, E. E., and Castle, W. B.: Experimental combined system disease, New England J. Med. **202**: 523, 1930.
18. Gordon, G., and Whitteridge, D.: Conduction time for human pain sensation, Lancet **2**: 700, 1943.
19. Gorman, W. F.: Alcoholic neuropsychiatric syndromes, Interne **6**: 152, 1949.
20. Gorman, W. F., Stearns, E., and Wortis, S. B.: The electroencephalogram in Korsakoff syndrome, Am. J. Psychiat. **107**: 20, 1950.
21. Greenfield, J. G., and Carmichael, E. A.: The peripheral nerves in cases of subacute continued degeneration of cord, Brain **58**: 483, 1935.
22. Grinker, R. R.: Some experiences with jake paralysis, Arch. Neurol. and Psychiat. **25**: 649, 1949.
23. Grinker, R. R., and Bucy, P.: Neurology, 1949, C. C. Thomas, Springfield, Illinois, p. 106.
24. Hall, B. F., and Campbell, D. C.: Pernicious anemia patient responding to vitamin B_{12} and normal human gastric juice, orally, Proc. Staff. Meet., Mayo Clin. **23**: 584, 1948.
25. Harvey, E. A., Howard, I., and Murphy, W. P.: Absence of toxic effect of folic acid on central nervous system of persons with pernicious anemia, New England J. Med. **242**: 446, 1950.
26. Jellinek, E. M., and Jolliffe, N.: Effects of alcohol on the individual, Quart. J. Stud. on Alcohol **1**: 110, 1940.
27. Jolliffe, N.: Effects of vitamin deficiency on mental and emotional processes, Proc. A. Research Nerv. and Ment. Dis. **19**: 144, 1939.
28. Jolliffe, N., Wortis, H., and Fein, D.: The Wernicke syndrome, Arch. Neurol. and Psychiat. **46**: 569, 1941.
29. Korsakow, S. S.: Ueber die alhohol Lähming (Russian), Moskau, 1887.
30. Korsakow, S. S.: Ueber eine besondere Form psychischer Störung kombiniert mit multipler Neuritis, Arch. f. Psychiat. u. Neurol. **21**: 669, 1890.
31. Moore, M., Raymond, A. F., and Gray, M. G.: Drugs and mental disease, Confinia neurol. **4**: 238, 1941.
32. Moore, M., Sohler, T., and Alexander, L.: Bromide intoxication, Confinia neurol. **3**: 1, 1940.
33. Nyswander, M.: Withdrawal treatment of drug addiction, New England J. Med. **242**: 128, 1950.
34. Rosenbaum, M., and Merritt, H. H.: Korsakoff syndrome, Arch. Neurol. and Psychiat. **41**: 978, 1939.
35. Smith, J. J.: Proceedings of the First Clinical ACTH Conference, 1950, Blakiston & Co., Philadelphia.
36. Smith, J. J.: Medical approach to problem drinking, Quart. J. Stud. on Alcohol **10**: 251, 1949.
37. Spies, T. D., Garcia Lopez, G., Milanes, F., Lopez Toca, R., and Aramburu, T.: A note on the oral versus parenteral administration of vitamin B_{12}, South. M. J. **42**: 528, 1949.
38. Tintera, J. W., and Lovell, H. W.: Endocrine treatment for alcoholism, Geriatrics **4**: 274, 1949.
39. Walker, J. T.: Toxicology, New England J. Med. **242**: 57, 1950.
40. Wartenberg, R.: Examination of reflexes, 1945, Year Book Publishers, Chicago, pp. 127, 128.
41. Wechsler, D.: *in* Wechsler, I. S.: Textbook of clinical neurology, 1943, W. B. Saunders & Co., Philadelphia, p. 204.

42. Weddell, G., and Sinclair, D. C.: Pins and needles, J. Neurol., Neurosurg. and Psychiat. 10: 26, 1947.
43. Wernicke, C.: Lehrbuch des Gehirnkrankheiten, vol. 2, 1881, T. Fischer, Berlin, p. 229.
44. Wilson, S. A. K.: Neurology, 1941, Williams & Wilkins Co., Baltimore, p. 700.
45. Wortis, H., Jolliffe, N., Stein, M. H., and Bueding, E. H.: Studies in Wernicke's syndrome, Tr. Am. Neurol. A. 67: 115, 1941.
46. Wortis, S. B., and Pfeffer, A. Z.: The management of alcoholism, Veterans Adm. Technical Bulletin, 10-67 Oct. 31, 1950.
47. Wortis, H., Stein, M. H., and Jolliffe, N.: Fiber dissociation in peripheral neuropathy, Arch. Int. Med. 69: 222, 1942.
48. Wortis, H., Wortis, S. B., and Marsh, F. I.: Vitamin studies in alcoholics, Am. J. Psychiat. 94: 891, 1938.
49. Zimmerman, H. M.: Newer aspects of nervous disease in avitaminosis, Confinia neurol. 1: 6, 1938.

CASE REPORTS

THE HAZARD OF CHOLINERGIC CRISIS DURING TREATMENT OF MYASTHENIA GRAVIS WITH OCTAMETHYL PYROPHOSPHORAMIDE *

By Charles W. Wilson, M.D., John P. Williams, M.D., F.A.C.P., and David H. Miller, M.S.(Biochem.), *Richmond, Virginia*

Octamethyl pyrophosphoramide (OMPA), a potent anticholinesterase, was first synthesized and shown to exhibit insecticidal activity by Schrader [1] in Germany in 1948. Studies by DuBois, Doull and Coon [2] revealed that this compound was converted by the liver into an agent which inhibited peripheral cholinesterase activity but had no effect on the brain cholinesterase, thus causing no symptoms referable to stimulation of the central nervous system. This selective peripheral action renders octamethyl pyrophosphoramide (OMPA) more desirable for the treatment of myasthenia gravis than those alkyl phosphates which inhibit both central and peripheral cholinesterase. Since atropine will not antagonize the central effects of the alkyl phosphates, it serves as a far more effective antidote for intoxication with OMPA. DuBois et al.[2] found the cholinesterase activity in tissues of rats to be for the most part irreversibly inactivated by OMPA and replaced only through formation of new enzyme. This concept was supported clinically by a case reported by Rider et al.,[3] in which the therapeutic effect was nonexistent one week after withdrawal of the drug; however, the cholinesterase activity of the serum and red cells was not back to normal 76 days after the last dose. The following case report demonstrates that this cumulative effect may produce toxic symptoms resulting in a fatality if not treated immediately with atropine.

Methods: OMPA and neostigmine (Prostigmin) were administered according to the method used by Rider et al.[3] Cholinesterase activity was measured manometrically with the Warburg apparatus, according to the method described by DuBois and Mangum.[4]

Case Report

A 57 year old white male textile worker developed ptosis of the eyelids in December, 1949. An ophthalmologist, with the aid of a positive neostigmine (Prostigmin) methylsulfate test, made the diagnosis of myasthenia gravis and referred him to

* Received for publication April 4, 1952.

From the Medical Service, McGuire Veterans Administration Hospital, Richmond, Virginia.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Octamethyl pyrophosphoramide for this study was supplied by Dr. C. G. Weigand, Head of Medical Department, Eli Lilly & Company.

an internist. The patient did not consult the doctor until September, 1950, when the ptosis had become disabling by obstructing his vision. His response to the administration of neostigmine (Prostigmin) bromide, 30 mg. orally every three to six hours, and ephedrine, 25 mg. twice daily, was good until July, 1951, when he had frequent attacks of nausea, vomiting and abdominal cramps. These side effects subsided with the change of the treatment program to neostigmine (Prostigmin) methylsulfate, 0.5 mg. intramuscularly before each meal, and neostigmine (Prostigmin) bromide, 30 mg. orally between meals and at bedtime as needed. In August, 1951, he began to notice increasing weakness and on September 1, 1951, he awoke quite ill, having dysphagia, dysarthria, difficulty with chewing, ptosis of the lids, more marked on the

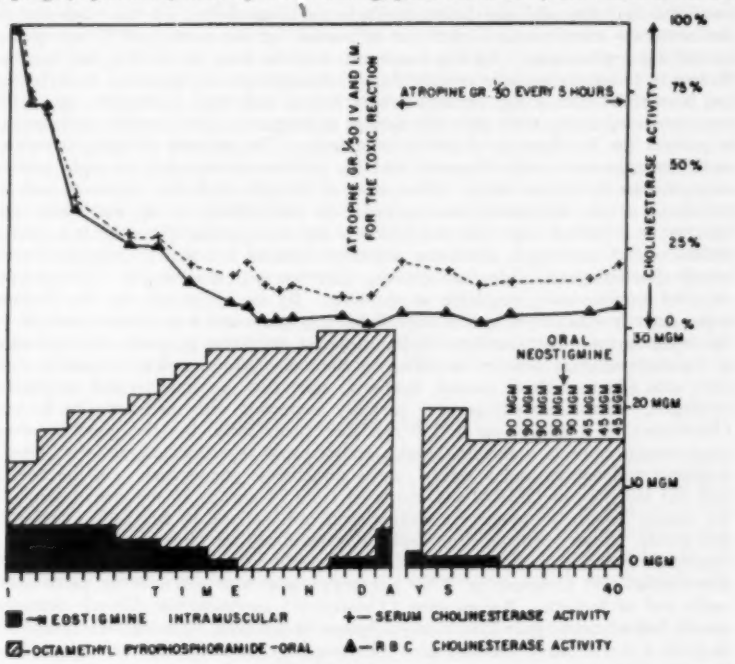


FIG. 1.

right, and diplopia. During the next 24 hour period he required 540 mg. of neostigmine (Prostigmin) bromide orally and 0.5 mg. neostigmine (Prostigmin) methylsulfate intramuscularly before each meal for survival. The symptoms continued to require a large number of neostigmine (Prostigmin) bromide tablets, which caused nausea, vomiting and abdominal cramps, so he resorted to neostigmine (Prostigmin) methylsulfate, 0.5 mg. intramuscularly every three hours. He was extremely weak on arrival at the hospital October 30, 1951, and required confinement to bed. The improvement from 1 mg. neostigmine (Prostigmin) methylsulfate intramuscularly every three hours was only fair and temporary. He had bilateral ptosis of the lids, weakness of convergence of the eyes and restriction of the eye movements in all directions. Because of paralysis of velum and uvula, attempts to swallow resulted in the expelling

of liquids through the nose. He awoke many times at night choking because he was unable to swallow the accumulated saliva. His speech was slurred and the facial weakness, as evidenced by a smooth forehead, everted lips and a myasthenic smile, was pronounced. In view of the poor response to increasing doses of neostigmine (Prostigmin) methylsulfate, we elected to give him one of the cholinergic phosphates. The course of therapy was regulated by the clinical response and by the depressant effect of OMPA on the serum and erythrocyte cholinesterase activity, as measured daily by the Warburg apparatus. On November 19, 1951, OMPA was started in a dose of 7 mg. by mouth at 9:00 a.m. and 9:00 p.m. daily, replacing the neostigmine (Prostigmin) methylsulfate usually given at these hours, but the latter drug was continued in a dose of 1 mg. intramuscularly six times daily. On the ninth day the cholinesterase activity was 19 per cent of normal for the serum and 10 per cent of normal for erythrocytes. By the fourteenth day the dose of OMPA had been increased to 14 mg. twice daily, and the dose of neostigmine (Prostigmin) methylsulfate had been reduced to 1 mg. intramuscularly before each meal. Atropine, gr. 1/100, was also given orally with each injection of neostigmine (Prostigmin) methylsulfate to prevent the development of abdominal cramps. The general strength, dysarthria and dysphagia were much improved and the patient was sleeping all night without strangulation by excess saliva. The ptosis of the lids had also improved and coordination of eye movements was normal. He was able to be up and about comfortably in a limited way. On the fifteenth day neostigmine (Prostigmin) methylsulfate was discontinued, since one injection induced a reaction characterized by muscle fasciculations, abdominal cramps, diarrhea and diaphoresis. The reaction subsided spontaneously, requiring no antidotes. By the eighteenth day the cholinesterase activity was 16 per cent of normal for the serum and 4 per cent of normal for the erythrocytes. The excellent clinical response paralleled generally the depression of the cholinesterase activity as shown by the daily Warburg determinations; however, side effects such as nausea, anorexia, salivation, lacrimation and diaphoresis developed. These side effects were partially controlled with methantheline bromide (Banthine), in a dosage up to 150 mg. four times daily, but the previous steady improvement came to a standstill and a rather rapid regression began, with marked weakness and nausea and a return of the myasthenic phenomena. On the twenty-first day the dose of OMPA was increased from 14 mg. to 15 mg. twice daily, but the patient became progressively weaker, with an increase in dysphagia, dysarthria and ptosis. Since methantheline bromide (Banthine) in large doses, or given to susceptible individuals, may cause a curare-like effect on the striated muscles, it was discontinued and atropine, gr. 1/50 intramuscularly, was given in its place before meals and at bedtime. Neostigmine (Prostigmin) methylsulfate, 0.5 mg. intramuscularly before meals, gave little if any response at this time. On the twenty-fifth day at 4:30 p.m., 1 mg. of neostigmine (Prostigmin) methylsulfate and gr. 1/50 of atropine intramuscularly had no effect, and by 7:00 p.m. the patient noted an increase in the generalized weakness, with inability to speak or swallow. The ward physician felt that the patient was suffering from myasthenic crisis and administered 0.75 mg. neostigmine (Prostigmin) methylsulfate intramuscularly at 7:30 p.m. The patient then developed marked prostration, lacrimation and diaphoresis; he could neither swallow nor expectorate, and had to hang his head over the side of the bed to allow the large quantities of saliva to flow from his mouth. Suction was started, and the nurse recalled the ward physician for further instructions. Certain that the patient was in myasthenic crisis, he increased the dose of neostigmine (Prostigmin) methylsulfate to 1 mg. intramuscularly at 8:15 p.m. and considered giving it intravenously but fortunately did not. Diaphoresis increased until the bed linens were wringing wet, and salivation was so profuse that the suction apparatus could not keep up with the flow of saliva. At 8:45 p.m., the patient was stuporous and having marked dif-

ficulty with respiration; consultation was requested (Dr. Wilson), and "cholinergic crisis" was immediately recognized. At 9:00 p.m. atropine, gr. 1/50, was given intravenously and intramuscularly, with immediate improvement. The patient was placed in an oxygen tent and by 10:00 p.m. was reasonably comfortable but did not become fully aroused until eight hours later. The intratracheal tube and Drinker respirator were kept close by for the next 24 hours but were not needed. Needless to say, all cholinergic medication was stopped and atropine, gr. 1/50 every four hours and as required, was continued for the next 36 hours, by which time all evidence of acute intoxication had disappeared. The cholinesterase activity during the period of intoxication was 15 per cent of normal for the serum and 3 per cent of normal for the erythrocytes. On the morning of the twenty-seventh day he was started on 0.5 mg. neostigmine (Prostigmin) methylsulfate before meals, and atropine gr. 1/50 was continued every five hours. On this low dosage myasthenic symptoms began to reappear, so on the twenty-ninth day, when the cholinesterase activity had risen to 20 per cent for serum and 6 per cent for erythrocytes, he was started on OMPA, 10 mg. night and morning. Nausea, salivation and diaphoresis recurred and were incompletely controlled by atropine, so the dose of OMPA was reduced to 8 mg. night and morning, where it has remained since. On the thirty-third day neostigmine (Prostigmin) bromide, 30 mg. (orally) 45 minutes before meals, was substituted for neostigmine (Prostigmin) methylsulfate, and as improvement continued this was reduced to 15 mg. (orally) 45 minutes before meals. It is entirely possible that this also might be dispensed with, but the patient, having used this drug for so long, is loath to give it up. It is planned later to observe the effect of placebo medication in its stead.

A glance at the accompanying graph will show that the serum and erythrocyte cholinesterase activity have stabilized at about 20 per cent and 6 per cent, respectively. The patient is relatively asymptomatic and is able to be up and about actively for at least six hours daily.

Comments and Summary

The early symptoms of acetylcholine intoxication in this case so closely simulated a so-called myasthenic crisis that resort to further anticholinesterase therapy seemed the logical course, as was probably true of the case reported by Rider et al.[3] What should have put us on guard immediately was the paradox that a patient with myasthenia gravis grew rather suddenly worse without coincidental precipitating cause on increasing doses of a medicine which had previously caused marked improvement.

As anticholinesterase therapy continued, on an emergency basis, the full blown picture of cholinergic intoxication developed, with extreme prostration, weakness and respiratory embarrassment, profuse sialorrhea and sudorrhea, excessive lacrimation and, finally stupor, which was relieved dramatically by intravenous and intramuscular atropine in large doses.

The generally accepted mechanism of the intoxication, as cited by Goodman and Gilman,[5] is that marked inactivation of the cholinesterase activity results in the preservation of acetylcholine in ganglia and end organs in striated muscle to such extent as to cause the paralytic phase of the nicotinic action and the excessive activity of smooth muscles and gland cells or muscarinic action.

It is obvious that when such a situation supervenes gradually during the therapy of myasthenia gravis with potent anticholinesterase preparations, occasions will arise frequently when the differentiation between "cholinergic crisis" and "myasthenic crisis" becomes a matter of life and death.

As with the differentiation between diabetic coma and dangerous hypoglycemia, the first prerequisite is an awareness on the part of the doctor of the physiologic mechanisms involved and the dangers inherent not only in the disease itself but also in its therapy. It might even be useful to speculate as to how many of the recorded "myasthenic crises" occurring under therapy and without recognizable provocation have in fact been "cholinergic crises."

Fortunately we have a very specific antidote for "cholinergic crisis" in atropine, which "prevents the mediator (acetylcholine) from penetrating the cell and reaching the receptive substance" of muscles and glands (Goodman and Gilman [5]). In our case the effect of intravenous atropine was so rapid and dramatic that all doubt as to the proper diagnosis was dispelled. This therapeutic test should be most valuable in the control of therapy.

Whatever danger there may be incident to the intravenous injection of atropine sulfate, gr. 1/50 would seem to be minimal. Colonel J. R. Wood et al.,[6] in their discussion of the treatment of nerve gas casualties which are, in fact, "cholinergic crises," state that atropine 2 mg. intravenously should be given every two or three minutes until evidence of atropinization is obvious. This dosage is greatly in excess of that required for the therapeutic test.

Warburg determinations of cholinesterase activity are of real value from the standpoint of research, but it is much too elaborate a procedure and the time lag much too great to make it a practical clinical aid. The parallel between depression of cholinesterase activity as shown by the accompanying graph and the gradual improvement of the patient was interesting; however, the degree of cholinesterase activity was of no aid in denoting the onset of the toxic reaction. The fact that the cholinesterase activity showed no appreciable change after the dose of the drug was reduced by one-half again supports the concept of cumulative action due to at least partially irreversible anticholinesterase activity. The last week of the graph is valuable in that it shows that the rate of inactivation or destruction of cholinesterase on the present dose of OMPA about equals the rate of reactivation or new production. This situation would seem to be ideal from a therapeutic standpoint. Whether it can be maintained throughout the changing vicissitudes of life is a question that further observation must answer.

Conclusions

1. OMPA is a potent anticholinesterase and a much more practical drug than those now in use in the treatment of myasthenia gravis.

2. As with all powerful drugs, there is danger of intoxication by overdose, as in this case, with the production of "cholinergic crisis" which may closely resemble "myasthenic crisis."

3. Differentiation of these two dangerous conditions on clinical grounds should not be too difficult if the following criteria are observed:

(A) Both doctor and patient should be fully aware of the superficial similarity between cholinergic and myasthenic crises.

(B) The paradox of regression without provocation on adequate or increasing medication should lead to strong suspicion of a cholinergic state.

(C) The coincidence of sialorrhea, sudorrhea and lacrimation, the muscarinic effects of acetylcholine, will tend to confirm the diagnosis of cholinergic state.

(D) The therapeutic test of atropine sulfate, gr. 1/50 intravenously, should cause rapid and marked improvement in the cholinergic state.

ADDENDUM

During the fourth month of treatment, while the patient was maintained on OMPA, 7 mg. every 12 hours, we substituted a placebo for each .25 mg. dose of neostigmine (Prostigmin) methylsulfate before meals. The patient continued to enjoy the meals without difficulty, and so was convinced that he did not require the neostigmine. At the present time he is ambulatory throughout the day, has no difficulty eating and sleeping, and is considering return to light duty in the mill.

ACKNOWLEDGMENT

We wish to express our gratitude to Dr. Harvey B. Haag, Professor of Pharmacology, Medical College of Virginia, for his advice and assistance in editing this report, and to Dr. Ernst Fischer, Research Professor of Physiology, Medical College of Virginia, for his assistance in the Warburg determinations.

BIBLIOGRAPHY

1. Schrader, G.: The development of new insecticides, final report. British Intell. Object. Sub-Comm., No. 714, rev'd 63, 1947, cited in Rider, J. A., and others.
2. DuBois, K. P., Doull, J., and Coon, J. M.: Studies on the toxicity and pharmacological action of octamethyl pyrophosphoramide, J. Pharmacol. and Exper. Therap. **99**: 376 (July) 1950.
3. Rider, J. A., Schulman, S., Richter, R. B., Moeller, H. C., and DuBois, K. P.: Treatment of myasthenia gravis with octamethyl pyrophosphoramide, J. A. M. A. **145**: 967 (March 31), 1951.
4. DuBois, K. P., and Mangum, G. H.: Effect of hexa-ethyltetraphosphate on cholinesterase in vitro and in vivo, Proc. Soc. Exper. Biol. and Med. **64**: 137 (Feb.) 1947.
5. Goodman, L., and Gilman, A.: The pharmacological basis of therapeutics, 1941, The Macmillan Co., New York.
6. Wood, J. R., Dickens, P. F., Jr., Rizzolo, J., and Bayliss, M. W.: Treatment of nerve-gas casualties, U. S. Armed Forces M. J. **2**: 1609 (Nov.) 1951.

MESENTERIC THROMBOSIS *

By W. T. McCOLLUM, M.D., F.A.C.P., *Oklahoma City, Oklahoma*

FICARRA [1] reviewed the literature on mesenteric vascular occlusion in 1944 and compiled about 554 cases; in addition, he reported 15 cases. In these and subsequent reports, there was no mention that a segment of colon had been passed per rectum. Two such cases constitute the basis of this report.

The segments consisted of a discontinuous tube composed of the major layers of the descending and sigmoid colon. Both patients passed formed stools per rectum after the catastrophe. In one, at the time of necropsy, a "new false colon" was found. This new channel was formed by remnants of the colon, the omentum, matted loops of small intestine and the parietal peritoneum (figure 1). The other patient had a similar intra-abdominal picture, was operated on, and is living and well.

The pathogenesis, pathology and clinical manifestations of mesenteric vascular occlusion are briefly discussed.

* Received for publication May, 2, 1951.

Case Reports

Case 1. A 79 year old white male had had prostatic obstruction for five and one-half years, and had had three transurethral resections for prostatic hyperplasia. He was admitted to the University Hospitals with complaints of dysuria, frequency and suprapubic pain of several days' duration.

Past History revealed "excision of an omental adhesion for intestinal obstruction (jejunal)" at 70 years of age.

Physical Examination revealed a well developed, poorly nourished, acutely ill elderly white male. The temperature was 101.8° F., pulse 108, respiration 18, and blood pressure 120/60 mm. of Hg. The skin was dry and the mucous membranes were pale. There were moderate arteriolosclerosis of the retinal arterioles and arcus senilis. Moderate bilateral costovertebral and suprapubic tenderness was elicited. The prostate was two to three times normal size, slightly tender, firm and smooth.

Laboratory Data: On admission, the urinalysis revealed a specific gravity of 1.014, 1 plus proteinuria and innumerable leukocytes. The hemogram was reported as 10.0 gm. hemoglobin, 4.1 million erythrocytes/cu. mm., and 11,500 leukocytes/cu. mm., with 73 per cent neutrophils.

Course in Hospital: The patient was given 15,000 units of penicillin every three hours, 1 gm. of sulfadiazine four times a day, parenteral fluids and an alkalinizing diuretic. The following day he complained of unusual thirst and became lethargic, irrational and "uncoöperative." On the fourth hospital day he developed incontinence of urine. The temperature, pulse and respirations had returned to normal by this time. On the eighth hospital day, the leukocyte count was 19,500, with 96 per cent neutrophils. The temperature became elevated to 101° F. (rectal). The pulse and respirations were normal, although there was no apparent improvement in the patient's condition. On the tenth hospital day, one examiner (Dr. Robert H. Bayley) noted a mass in the left lower quadrant which was continuous with the urinary bladder. Surgical exploration was advised. There were no significant urinary findings, and the blood non-protein nitrogen was 40 mg. per cent. The total plasma proteins were 5.1 gm. A septic temperature curve continued, with the peaks at 102° F. The pulse was proportionate. Intravenous and retrograde urograms revealed no significant abnormality. On the thirtieth hospital day, a segment of the colon, 41 cm. in length, in the form of a discontinuous tube, was passed per rectum. The specimen consisted for the most part of colonic mucosa, submucosa and muscularis. Histopathologic examination revealed typical coagulation necrosis. Immediately following this episode, respirations increased, and mild cyanosis and "discomfort" in the chest were noted. A diagnosis of pulmonary embolism was considered. The stools were loose and watery and of increased number (10 to 15 a day). Three days later (thirty-third hospital day), the stools again became formed. The temperature and pulse continued to be of septic type, and the patient's course continued essentially unchanged until the fifty-second hospital day, when he suddenly became cyanotic. The pulse was "weak" and fast (120 to 130 per minute). The blood pressure dropped to 90/50 mm. of Hg. He became comatose, passed a large, soft, formed stool involuntarily, and died.

Pertinent Postmortem Findings (figure 1): A large mass occupied the left abdomen and surrounded the colon, extending from a point 5 cm. below the splenic flexure to the rectosigmoid juncture. Within this mass, the descending and sigmoid colon was discontinuous; however, a new passageway had been established connecting the proximal descending colon and the rectosigmoid juncture. From above downward, the anterior and lateral portions of the colon were missing for a distance of 10 cm., with only an irregular strip of the posterior wall, approximately 2 cm. wide, remaining. This was composed of muscular coat and serosa. Those structures which

replaced the missing wall were made up (from above downward) of the omentum, adherent loops of terminal jejunum and parietal peritoneum of the lateral abdominal wall. This false passageway continued distally for 10 cm., at which point there was a circular band of colon composed of muscularis and serosa, 1 cm. in length. Distal to this, the colon again became discontinuous, i.e., only the posterior wall remained, and that was denuded of its mucosa. It extended in this manner for a distance of 12 cm., at which point the muscular and serosal walls of the colon again became in-

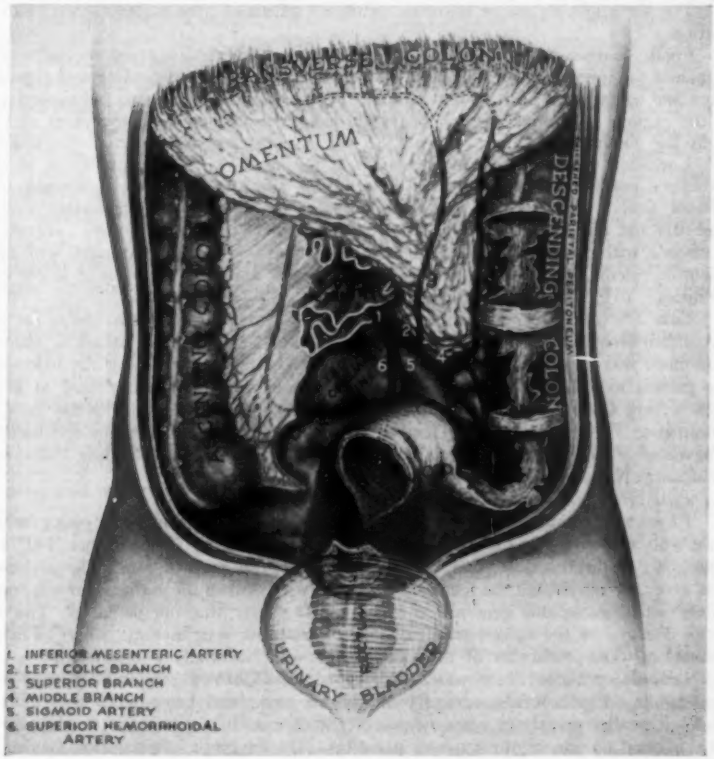


FIG. 1.

tact, forming a tubular structure 4.5 cm. long. Distal to this, the colon was entirely missing. Its place was occupied by a globular cavity, 8 cm. in diameter, formed by the serosal surface of adherent loops of jejunum on the right and anteriorly, the posterior surface of the urinary bladder and the parietal peritoneum, inferiorly and on the left. The inner surface was made up of gangrenous tissue. The rectum protruded from the inferior surface of this cavity and afforded an outlet for the "new false colon." A formed soft stool was present in the rectum. The superior mesenteric artery was patent throughout, as was the superior hemorrhoidal branch of the

inferior mesenteric artery. The superior branch of the left colic artery was barely patent. The middle and sigmoid branches of the left colic artery were completely occluded by organized thrombus. This thrombus extended to within 3 or 4 cm. of the origin of the left colic artery. The mucosa of the cecum and ascending and transverse colon was normal. There was a solitary abscess, 3 cm. in diameter, in the left lobe of the liver.

A massive thrombotic embolus occluded the pulmonary artery and its branches. Thrombi were present in the veins of the right leg.

The aorta and its major branches exhibited advanced atherosclerosis with calcification.

Final Anatomic Diagnosis: (1) Mesenteric thrombosis involving the left colic branch of the inferior mesenteric artery, with infarction of the descending and sigmoid colon and coagulation necrosis and "slough" of the mucosa, submucosa and muscularis in the region. (2) Massive pulmonary thrombotic embolism from the veins of the right leg (immediate cause of death). (3) Atherosclerosis, generalized, marked. (4) Localized peritonitis, fibrinopurulent and fibrous. (5) Thrombophlebitis of intrahepatic portal veins, with an area of infarction and a solitary hepatic abscess, left lobe of liver. (6) Hyperplasia of the prostate. (7) Chronic suppurative pyelonephritis and ureteritis, especially left, and cystitis. (8) Chronic passive congestion of viscera, with confluent hypostatic bronchopneumonia. (9) Septic splenitis with episplenitis, calcific, focal. (10) Emaciation, moderate, and pitting edema of lower extremities. (11) Chronic cholecystitis.

*Case 2.** A 33 year old white male had had several injection treatments for internal hemorrhoids in which quinine-urea was used. On the last occasion, sodium morrhuate was used as the sclerosing agent. A few minutes following the injection, the patient experienced generalized abdominal pain which, although mild at first, became very severe after an hour. The pain persisted and the following day he was admitted to Wesley Hospital in Oklahoma City. The pain was constant and became progressively more severe. It was particularly marked in the right upper abdominal quadrant. No nausea, vomiting or diarrhea was observed.

Past History: Noncontributory.

Physical Examination revealed a well developed, well nourished young white male who was obviously experiencing severe abdominal pain. Temperature, 102° F.; pulse, 96; respirations, 20, and blood pressure, 160/96 mm. of Hg. The abdomen was generally tender, but the tenderness was more marked in the right upper quadrant. There was questionable generalized rigidity. The liver was not palpable. The inferior margin of the spleen was palpable. Peristalsis was absent. There was no distention. The remainder of the examination was essentially noncontributory.

Laboratory Data: There was a leukocytosis of 24,900/cu. mm., with 82 per cent neutrophils. Erythrocytes were 4.4 million/cu. mm., and hemoglobin was 85 per cent. Repeated urinalyses were negative. Stool examination on the third hospital day revealed no pus, erythrocytes or parasites. On the tenth hospital day, the leukocyte count was 31,200/cu. mm., with 84 per cent neutrophils (27 per cent nonsegmented forms). The hemoglobin was 86 per cent and the erythrocyte count was 4.36 million/cu. mm. Five days later (the fifteenth hospital day), the white count had declined to 16,300, with 67 per cent neutrophils, and it remained essentially unchanged for the duration of the hospital course.

Course in Hospital: Morphine did not give complete relief from the abdominal pain. On the fourth hospital day, peristaltic sounds were audible, although markedly decreased. At this time there was marked abdominal distention. The generalized

* We are indebted to Dr. Raymond L. Murdoch, Oklahoma City, Oklahoma, for permitting us to report this case.

tenderness had subsided. There was marked tenderness of the left quadrants. On the tenth hospital day a marked diarrhea developed, accompanied by generalized abdominal cramping pains. Three days later, "a piece of tissue" was passed per rectum. On the nineteenth hospital day, a 66 cm. "cast of colon" was passed per rectum. This consisted of colon mucosa, submucosa and muscularis. Histopathologic examination revealed typical coagulation necrosis. By the fortieth hospital day, small, soft, brown, rather well-formed stools were passed intermittently with the loose watery stools. The patient was discharged from the hospital on the forty-third day of illness.

His condition was satisfactory for six weeks. At this time he was rehospitalized because of a rather abrupt recurrence of generalized abdominal cramps, with generalized abdominal tenderness, particularly along the left colon. His abdomen was distended and his temperature was 100° F. There was a leukocytosis of 26,200 with 64 per cent neutrophils (25 per cent nonsegmented forms). A cecostomy and appendectomy * were performed on the fourth hospital day. The postoperative course was uneventful, and on the twenty-third hospital day a left colectomy was done, bringing the splenic flexure out as a "single-barrel colostomy." The descending and sigmoid colon was removed. This consisted of a discontinuous, thin-walled tube. The postoperative course was uneventful except that on the nineteenth postoperative day signs and symptoms of intestinal obstruction developed. A laparotomy disclosed an adhesion obstructing the terminal jejunum. This obstruction was relieved. The cecostomy tube was removed and the stoma healed. The patient was discharged on the seventy-first hospital day (five months and four days following the injection of the sodium morrhuate), at which time the colostomy was functioning normally.

The patient was seen again 14 months later. He had gained 40 pounds, and had been working since two and one-half months after discharge from the hospital. He had been quite active, and apparently had been well until four days previously, when he noted right-sided abdominal pain that required morphine for relief. Symptoms and signs were indicative of intestinal obstruction. A third operation was performed and an adhesion obstructing the lower ileum was removed. The immediate postoperative and subsequent course (eight and one-half years) has been uneventful.

Discussion

Pathologic Considerations: The incidence of the involvement of the various arteries and veins and the underlying etiology are at variance to some extent in the literature.

Embolism: Emboli involve the superior mesenteric artery, since there is a continuation of the flow of blood from the aorta to this artery.[2, 3] These emboli usually arise from vegetations on the heart valves in acute or subacute bacterial endocarditis, from mural thrombi in the left ventricular cavity associated with myocardial infarction, or from thrombi in the left atrial cavity in arrhythmias, or from atheromatous plaques breaking off from the wall of the aorta.

Venous Thrombosis: Whittaker and Pemberton [4] were of the opinion that thrombosis when it occurred more commonly involved the mesenteric veins; however, Trotter [5] and Larsen [6] felt that the arteries were more commonly involved.

Primary venous thrombosis of the mesenteric veins is quite rare and, when it occurs, is due to endophlebitis and phlebosclerosis.[2]

* This operative procedure performed by Raymond L. Murdoch, M.D., Oklahoma City, Oklahoma.

Berry and Bougas [6] reported 13 instances in 12 patients. These cases were felt to be of the primary venous type and were referred to as agnogenic venous thrombosis. Appendicitis, strangulation, etc., were not apparent causes in the cases reported.

Secondary venous thrombosis is usually due to liver diseases or pylethrombophlebitis, the result of infection of the viscera that are tributaries of the portal vein, e.g., appendicitis, inflammatory pelvic disease and infected ulcerating carcinomas of the colon. Congestive heart failure is commonly associated with venous thrombosis.[8] When secondary venous thrombosis is not due to inflammation, injury to the vessels from mechanical means is usually at fault, e..g, constrictions due to a strangulated hernia, operative trauma or postoperative adhesions. Boyd[2] was of the opinion that thrombosis of the inferior mesenteric vein did not cause death. Case 2, reported herein, would certainly substantiate this view, since the site of thrombosis is known and since (unavoidably from the surgical standpoint) surgery was postponed a considerable length of time without fatality. However, there is not complete agreement on this point.[1]

Arterial Thrombosis: This is usually associated with arteriosclerosis [7] (atherosclerosis) and/or heart failure.[8] In the former case, the usual processes seen in arterial thrombosis are at fault. There may be occlusion of the artery by a large atheromatous plaque, or hemorrhage under a plaque, or the plaque may break off and occlude the vessel (as mentioned above) at a distal point. Thrombosis is also seen in polycythemia rubra vera, leukemia and splenic anemia. Specific vascular diseases recorded as to having caused arterial thrombosis are Buerger's disease,[9] Raynaud's disease [10] and mesenteric arteriosclerosis. Rives, Strug and Essig [8] reported a case due to disseminated lupus erythematosus.

Whipple's intestinal lipodystrophy has been reported as a cause of mesenteric thrombosis.[9, 11, 12]

Pathogenesis of Hemorrhagic Infarction of the Intestine: Virchow reported that the hemorrhage was the result of reflux flow of blood from the veins, but the pathogenesis of mesenteric occlusion has been debated. Boyd [2] produced vascular occlusion experimentally and noted ischemia first. This was followed by violent contractions of the intestine which resulted in an exaggeration of the ischemia. Death of the part followed. Welch and Mall [13] felt that the hemorrhage was due to reflux of arterial blood which came by way of collaterals. Laufman [14] felt that both views were in part correct. When arterial and venous ligations are performed, there is redistribution of the blood in the vascular tree, plus regurgitation or reflux from collaterals.

Pathology: The pathologic change seen in mesenteric vascular occlusion varies with the location of the occlusion. From a practical standpoint there is little difference in the change, whether the occlusion be arterial or venous. The age of the process and the size of the vessel occluded are the main factors influencing the extent of the process. If the condition is diagnosed and operative removal of the segment of the intestine accomplished early, there will be edema and varying degrees of hyperemia. This is followed by extensive hyperemia, petechial hemorrhages and necrosis with ulceration. Coagulation necrosis with ulceration, perforation and peritonitis is usually the final result. There will be found bloody fluid in the peritoneal cavity and blood within the intestinal lumen. The mucosa is affected first by coagulation necrosis, since it is the most sensitive

to loss of blood supply. This sensitivity progressively decreases in the submucosa, muscularis and serosa. Coagulation necrosis typically gives a "ghost-like" appearance to the tissues, with the normal architecture remaining faintly discernible.

Age and Sex: The age distribution of mesenteric vascular occlusion, as recorded in the literature, ranged from a 10 day old infant [15] to an 84 year old adult.[16] It is generally agreed that the greatest incidence occurs in the fifth and sixth decades of life. Trotter,[3] in his monograph, reported 360 cases; 62 per cent of the cases were males, 38 per cent females.

Clinical Considerations: The clinical features of mesenteric vascular occlusion so closely simulate those seen in numerous other abdominal conditions that only a brief consideration of the signs and symptoms will be undertaken. Emphasis must be placed on the consideration of this entity in the differential diagnosis of abdominal cases. This alone will lead to many correct early diagnoses.

The pain can be sudden or gradual in onset, severe or mild in intensity, and localized to the midabdomen or lower abdomen or generalized. Temperature, blood pressure, pulse and pallor depend upon the presence or absence and the degree of shock. When recorded early, the temperature and blood pressure are usually normal or subnormal. Later, the temperature is usually septic and the pulse is proportionate. Nausea and vomiting occur in a certain number of cases. It is the opinion of Whittaker and Pemberton [4] that vomiting is more common in arterial occlusion and that, when arterial and venous occlusion occur together, vomiting will be seen in 75 per cent of the cases. Warren and Eberhard,[17] from their analysis, considered vomiting quite diagnostic. Tenesmus and blood in the stools are also variable as diagnostic points, though important when seen. Rigidity and localized tenderness are unusual. Distention and flaccidity of the abdominal wall are common, especially late. A palpable mass is seen in only a small percentage of cases.

Laboratory Considerations: The laboratory is of little assistance as a diagnostic measure. There is usually a rather marked leukocytosis (averaging 20,000 to 30,000), with a predominance of neutrophils. Roentgenograms of the abdomen may show signs of ileus or intestinal obstruction. Barium studies are not feasible.

Therapeutic Considerations: Treatment of mesenteric vascular occlusion rests with surgical intervention, supplemented by adequate therapeutic anticoagulant therapy. It is not within the scope of this paper to discuss the merits of surgical technics or approaches to the problem. Wangensteen [18] presents data on cases in which varying lengths of small intestine have been removed. One can conclude that excision of up to one-third of the small intestine is well tolerated by adults; infants and children, however, do not tolerate excessive resections so well as adults. There is usually some degree of debilitation following these resections. The recovery, however, is progressive and uneventful. Tolerance to fats is decreased. Doerfler [19] performed a resection in a patient, leaving only 32 cm. of small intestine, and the patient was living and in good health six and one-half years later. Resection of rather large portions of the colon are well tolerated. Stool habits change, usually increasing in number. With adjustment of the type of food intake, the patient can frequently control the type and number of stools per day.

SUMMARY

The etiology, pathogenesis, pathology and clinical aspects of mesenteric vascular occlusion are discussed. Mesenteric occlusion occurs in all age groups, but is more common in older patients. The superior mesenteric vessels are more frequently involved. The inferior mesenteric vessels are rare sites of vascular occlusion.

Two cases are presented in which a segment of the descending and sigmoid colon, consisting of mucosa, submucosa and portions of muscularis and serosa, was passed per rectum. The remaining portions of colon were reinforced by omentum, loops of small intestine and parietal peritoneum of the abdominal wall to form a new "false colon" and the patients passed formed stools per rectum following the vascular occlusions. In case 1, the process was due to thrombosis of the inferior mesenteric artery. The patient died from thrombotic embolism of the pulmonary arteries. In case 2, the vein was obviously involved.

In the final analysis, *the diagnosis rests upon the consideration of mesenteric vascular occlusion* in the differential diagnosis of abdominal conditions, acute or chronic.

The treatment is surgical intervention, supplemented by adequate therapeutic anticoagulant therapy.

ACKNOWLEDGMENT

Sincere appreciation is expressed to Dr. Howard C. Hopps, Dr. Robert H. Bayley and Dr. W. Floyd Keller for their helpful suggestions in the preparations of this paper; to Mr. E. F. Hiser, Assistant Professor, Department of Medical Illustration, for his excellent reproduction, and to Mrs. Bobbie Antrim for her stenographic assistance.

BIBLIOGRAPHY

1. Ficarra, B. J.: Mesenteric vascular occlusion, Am. J. Surg. **66**: 168, 1944.
2. Boyd, W.: Surgical pathology, 5th ed., 1942, W. B. Saunders Co., Philadelphia.
3. Trotter, G.: Embolism and thrombosis of mesenteric vessels, 1913, Cambridge University Press, London.
4. Whittaker, L. D., and Pemberton, J. de J.: Mesenteric vascular occlusion, J. A. M. A. **111**: 21, 1938.
5. Larsen, G. M.: Mesenteric vascular occlusion, Surg., Gynec. and Obst. **53**: 45, 1931.
6. Berry, F. B., and Bougas, J. A.: Agnogenic venous mesenteric thrombosis, Ann. Surg. **132**: 450, 1950.
7. Conner, L.: Arterial thrombosis in visceral disease, Am. J. M. Sc. **135**: 13, 1933.
8. Rives, J. D., Strug, L. H., and Essig, I. M.: Mesenteric vascular occlusion, Ann. Surg. **127**: 887, 1948.
9. Garvin, E. J.: Mesenteric vascular occlusion complicating thromboangiitis obliterans, Am. J. Surg. **74**: 211, 1947.
10. Mitchell, J. F.: Mesenteric thrombosis, Ann. Surg. **77**: 299, 1923.
11. Pemberton, de J., Comfort, M. W., Fair, E., and Zaslow, J.: Intestinal lipodystrophy; Whipple's disease, Surg., Gynec. and Obst. **85**: 85, 1947.
12. Whipple, G. H.: A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymph tissues, Bull. Johns Hopkins Hosp. **18**: 382, 1907.
13. Welch, W., and Mall, F.: *In* Abott's System of medicine, Vol. 6, Macmillan Company.
14. Laufman, H.: The effect of heparin on the behaviour of infarction of the intestine, Surg., Gynec. and Obst. **74**: 479, 1942.

15. Laufman, H., and Scheinberg, S.: Arterial and venous mesenteric occlusion, Am. J. Surg. 58: 84, 1942.
16. Jackson, J. M., Allen, C. A., and Quimby, W. C.: Mesenteric embolism, and thrombosis, J. A. M. A. 42: 1469, 1904; 43: 25, 1904; 43: 110, 1904; 43: 183, 1904.
17. Warren, S., and Eberhard, T. P.: Mesenteric venous thrombosis, Surg., Gynec. and Obst. 61: 102, 1935.
18. Wangensteen, O. W.: Intestinal obstruction, 2nd ed., 1942, Charles C Thomas, Springfield, Illinois.
19. Doerfler, H.: Kann der Mensch ohne Dünndarm leben? Zentralbl. f. Chir. 50: 1502, 1923.

ALBRIGHT'S SYNDROME *

By RALPH E. HIBBS, M.D., F.A.C.P., *Medford, Oregon*, and
HOMER P. RUSH, M.D., F.A.C.P., *Portland, Oregon*

ALBRIGHT'S syndrome [1] is characterized by brown pigmentation of the skin, a cystic disease of the bone and precocious puberty, in females. It is a rare disease—less than 50 cases of the complete syndrome have been reported to date. Other terms used to describe this disease include polyostotic fibrous dysplasia, brown spot syndrome and osteitis fibrosa disseminata. Its importance lies in the recognition of the bone lesions and their differentiation from those of hyperparathyroidism and other cystic diseases of the bone. If Albright's syndrome is present, an operation on the parathyroids can be avoided, since these glands are not involved in this process. We report an additional typical case.

CASE REPORT

A 46 year old white female was first seen in our office on February 18, 1949, complaining of a pain in the left chest. The pain was sharp, shooting and intermittent; it radiated into the left shoulder and was not related to exertion or gastrointestinal function.

Past history was remarkable in that her menstrual flow began at six months of age. It was of four to five days' duration, 28 day cycle. She recalls no menstrual cramps. Pubic and axillary hair had been present as far back as she could remember. "I grew up with hair on my body." Patient grew rapidly and "was the largest one in my group" during childhood. Growth stopped at 11 or 12 years—"Soon every one passed me by"—so that she was the smallest one in her group in her teens. At nine years of age a fall from a swing fractured the left zygomatic process. Healing was rapid and satisfactory. At 12 years, her third molars had erupted. Her dentist remarked, "You must be older than your stated age." At 14 years the left femur was fractured by a fall while patient was pole-vaulting. Four years later, when she was 18, a car struck the left side of her chest and fractured three or four ribs. When 26 years old, she fell while running and fractured the neck of the left femur. The last fracture, in 1933 when patient was 31 years old, was of the neck of the left femur again, caused by her jumping off a box. All of these fractures healed promptly, but with some deformities.

* Received for publication December 27, 1950.
From the Department of Medicine, University of Oregon Medical School.

Patient was admitted to St. Vincent's Hospital for reduction of this last fracture on May 29, 1933. X-rays taken at that time were reported as follows:

"There is an osteitis fibrosa cystica process involving both ilia, and the head and the shaft of the left femur, and the head and the neck of the right femur. There is also an involvement of the left tibia with marked widening of the bone at the middle of the shaft, with cystic degeneration along the shaft. There is widening of the shaft of the fibula, widening of the shaft of the right tibia, but no cystic changes. There is osteitis fibrosa cystica of the tenth rib posteriorly on the left side and of the sternum."

Laboratory Findings: Serum calcium, 11 mg. per cent (normal, 9 to 11 mg. per cent); urinary calcium, 0.241 gm. in 3,900 c.c. urine (normal, 0.1 to 0.5); hemoglobin, 98 per cent; red blood cells, 4.70; white blood cells, 9,300; 51 per cent polymorphonuclears, 1 monocyte, 47 per cent small lymphocytes. Serology, negative. Stool for occult blood, negative.

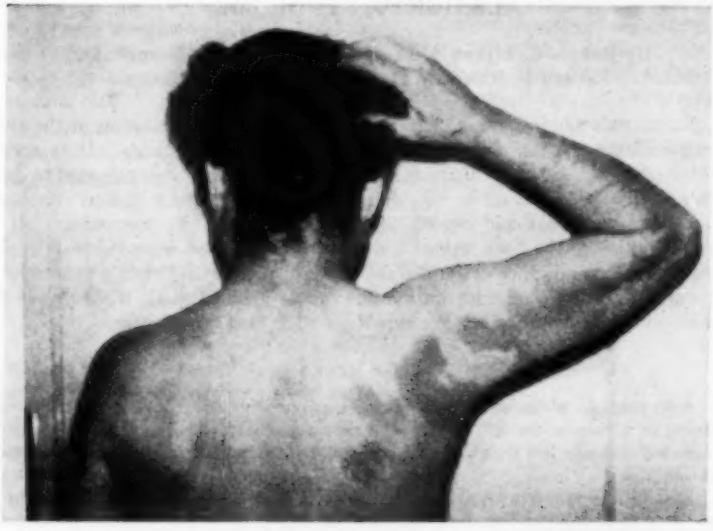


FIG. 1. Note areas of brown pigmentation with jagged border.

Examination at that time revealed a short stature, and bony deformities of the face and left leg.

On June 6 two "large parathyroid glands were exposed on the left. These, with part of the left lobe of the thyroid, were removed. No parathyroids were seen on the right." The pathologic diagnosis was "diffuse hyperplasia of parathyroid gland." Serum calcium on June 11, 1933 (five days postoperative) was 12 mg. per cent. The course was uneventful and she was discharged as cured. X-rays taken of cystic lesions in 1934 and 1935 showed "marked improvement."

In 1935 she was admitted to the obstetrical department with her first pregnancy. Because of deformities of the pelvis, a Cesarean section was performed and a normal baby girl delivered.

Additional questioning concerning her past history revealed that the brown pigmented spots on the right shoulder and arm had been present all her life. There was no history of any neurologic disease. Her school work had been above average. There was no history of liver disease or jaundice in the past.

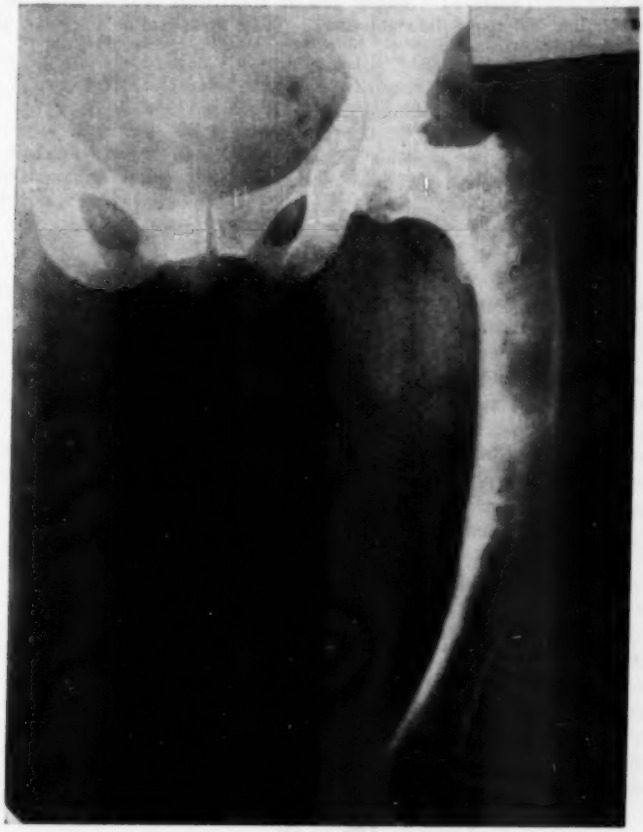


FIG. 2. Note cystic areas in left femur and around acetabulum. The outward bowing and irregular architecture of femur are result of three old fractures.

Family history was noncontributory except that the patient had had a twin brother who had died of meningitis at the age of seven years.

Marital History: Husband alive and well at 50 years. Gravida, one; child is now 13 years and in good health. The daughter started menstruating at 13 years; she shows no pigmentation of the skin or precocious development. In August, 1947, because of a fall, the daughter had x-rays taken of left radius which revealed a fusi-

form swelling 2 cm. in length involving the upper end of the left radius. The bone cortex was intact; a biopsy of the cyst was reported as "polyostotic fibrous dysplasia."

Physical examination of the patient on February 18, 1949, revealed a stocky female in apparent good health. Weight, 168 pounds; height, 5 feet. There was one large brown pigmentation of the skin covering the posterior aspects of the right shoulder and arm (figure 1). Several smaller areas were present along the neck and the hair line and above the right elbow. These areas had an irregular, jagged

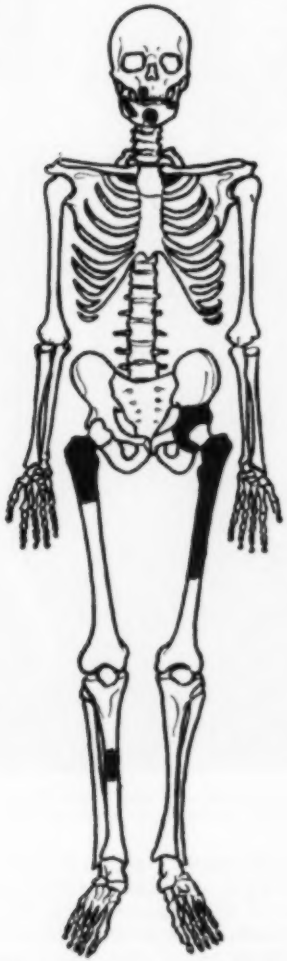


FIG. 3. Skeletal diagram showing location of bone cysts.

border. Bony deformities of the left zygomatic process were present, and also foreshortening and outward bowing of the left femur. Blood pressure was 120/70 mm. of Hg. A soft systolic murmur was heard at the apex of the heart. Lungs were clear; abdomen was negative. The reflexes were present and equal on both sides.

Laboratory Data: Urine: pale yellow, clear; pH, 6.0; specific gravity, 1.003; negative for albumin, sugar, acetone, pus; 1 to 2 white blood cells per high power field; epithelial cells, few. Blood: 83 per cent hemoglobin, 11.48 gm.; red blood cells, 3,650,000; white blood cells, 9,100; color index, 1.10; polymorphonuclears, 68; staff cells, 2; lymphocytes, 28; monocytes, 2; sedimentation rate, 3/22. Fluoroscopy: normal heart and lungs. Kolmer test: negative in all antigens. Kahn test: 1 plus and 2 plus. Cardiolipin: negative. Blood cholesterol: 290 mg./100 c.c. Alkaline phosphatase: 1.1. Bodansky units. Phosphorus: 2.9 mg. Calcium: 9.8 mg. Complete skeletal x-rays showed the lesions located as described in 1933. The cysts in the ribs revealed definite progression in size (figures 2 and 3).

Comment

This case qualifies as an example of Albright's syndrome.[2] The notation of parathyroid surgery, commonly found in these patients and present in this case, is not surprising, since surgery was done in 1933 and the first description of this syndrome was not published until 1937. The serum calcium and urinary excretion studies were done preoperatively and showed no parathyroid dysfunction.

It should also be pointed out that the pigmentation of the skin of this patient was confined to the right side of the body, while the bone lesions were predominantly on the left side. This is not usual, nor is the progression of the bone cysts during adulthood. Another interesting feature of this case is the fact that the patient's daughter also showed a cyst of the bone, and biopsy was typical of polyostotic fibrous dysplasia.

The blood chemistry studies, done immediately following the parathyroid surgery, were not altered toward the low side. In fact, the calcium was 12 mg. per cent after surgery, compared to 11 mg. per cent before surgery. Sixteen years later, the level was 9.8 mg. per cent. In other words, enough parathyroid tissue remained to satisfy normal metabolic requirements. The significance of the pathologic diagnosis of "diffuse hyperplasia of parathyroid gland" from the biopsy is not clear. There is no evidence available to indicate that the patient had any disease of her parathyroids. We question whether the histopathology of the parathyroids was sufficiently understood in 1933 definitely to establish that diagnosis.

Discussion

Since the original description by Albright [1] in 1937, many cases have been reported,[3] but not all of these contain the entire triad. Lichtenstein and Jaffee [4] suggest that the bone lesions are the primary finding, and that brown spots and endocrine disorders may be lacking in certain cases. In our case, the only factor transmitted to the child was the bone lesions. Hereditary factors may account for the bone cysts; the remaining features are less frequently transmitted. We have seen a case of this type. She was studied because of cystic degeneration of

the right pelvic region. X-rays showed cysts in the right ilium, femur, tibia and foot. No brown spots of skin were found. Menses began at 12 years.

The pigmentation is cafe-au-lait in color, with an irregular, sawtoothed border. The spots are localized curiously to one side of the body, usually the same side as the bone cysts. The back, neck, scalp and thighs are the most frequent sites. Biopsy reveals the pigment to be melanin in the basal layer of the epidermis and even into the granulosum.

The bone cysts, polyostotic fibrous dysplasia, are always multiple, and have a predilection for the lower extremities. The uppers are less frequently involved. Characteristically, the cysts are segmental in distribution, and confined to the same side as the pigmentation. The femur, pelvis, ribs, skull, tibia and humerus are the most frequent sites. However, no bones escape entirely if the process is disseminated. Apparently present from birth, they are usually not recognized until childhood or early adult life incidental to a fracture. Growth of the cysts seems to stop almost entirely after cessation of skeletal growth. Pathologic fractures may occur if the cortex is thinned sufficiently by the expanding cyst. Periosteal reaction is usually absent. The epiphysis is not usually involved, in contradistinction to dyschondroplasia. Fractures through the cyst heal promptly but may lead to severe deformities. Normal bone is present between the cysts. The generalized decalcification seen in hyperparathyroidism is missing; in fact, areas of sclerotic bone may at times be found between the fibrous cysts. The lamina dura, invariably involved in the bone disease of hyperparathyroidism, is unaffected in this syndrome.

The gonadal dysfunction consists of precocious sexual development in females, but usually not in males. Menses may start at a very early age (six months in our patient). This syndrome is one of the causes of true pubertas precox in females. There is no impairment of fertility. In fact, there have been some claims that the fertility index of these patients is very high. Their skeletal growth is so accelerated that they will be large for their age during childhood. There are an early ripening of the epiphysis and a premature arrest of growth. Consequently, these patients are usually short when full stature is attained. This precocity is usually not found in males, but Albright [6] found one boy who showed slight advancement of somatic growth, the only case of disturbed growth pattern in a male with this syndrome to come to our attention.

Blood chemistry studies reveal normal calcium and phosphorus levels. A few cases have been reported with high normal values for calcium and even slight depression of phosphorus. Garlock [5] reported a proved case of polyostotic fibrous dysplasia with blood calcium of 13 mg. per cent, phosphorus 2.8 mg. per cent, and a negative calcium balance. Nevertheless, the chemical imbalance never assumes the proportions seen in hyperparathyroidism. Alkaline phosphatase is elevated as long as activity exists in the bone lesions.

Differential diagnosis must exclude the following diseases of bone: osteitis fibrosa cystica of hyperthyroidism, eosinophilic granuloma or xanthoma, multiple myelomatous lesions of the bone, neurofibromatosis, metastatic neoplasm, hemangioma, Paget's disease and giant cell tumor. Granulosa cell tumor of the ovary causes pubertas precox but is distinguished by the absence of pigmentation

and bone cysts. Cafe-au-lait pigmentation of the skin occurs frequently as birthmarks but is seldom associated with the other features. The diagnosis depends [5] upon the presence of premature sexual development in females, large brown areas of pigmentation of the skin, x-ray evidence of bone cysts in segmental distribution and, finally, normal blood chemistry determinations.

The cause of this disease is not known. Albright [6] feels that the primary disturbance of this malady is in the central nervous system, possibly in the region of the hypothalamus. He bases his opinion on the fact that bone cysts have a segmental distribution corresponding to the spinal nerves. Also, the endocrinopathy may be the result of an interruption of the normal afferent impulses traveling to the pituitary gland. Our patient showed no neurologic disturbance.

There is no treatment other than orthopedic correction of the deformities. The disease is not fatal. The fractures are the only problems requiring attention. Aluminum acetate,[7] calcium and vitamin D and x-ray therapy, to induce calcification in the cysts, have been tried without demonstrable benefit.

Summary

1. Cystic disease of the bone, brown spots on the skin and pubertas precox, if occurring in females, have been described as Albright's syndrome and do not require parathyroid surgery.

2. An example of Albright's syndrome is presented in which typical bone lesions were transmitted to the daughter.

BIBLIOGRAPHY

1. Albright, F., Butler, A. M., Hampton, A. O., and Smith, P.: Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation, and endocrine dysfunction with precocious puberty in females, New England J. Med. **216**: 17, 1937.
2. Albright, F.: Personal communication. These X-rays were reviewed by Dr. Albright, who thought they undoubtedly represented polyostotic fibrous dysplasia.
3. Dockerty, M. B., Ghormley, R. K., Kennedy, R. L. J., and Pugh, D. G.: Polyostotic fibrous dysplasia, Arch. Int. Med. **75**: 357 (June) 1945.
4. Lichtenstein, L., and Jaffee, H. L.: Fibrous dysplasia of bone: a condition affecting one, several or many bones, the graver cases of which may present abnormal pigmentation of skin, premature sexual development, hyperthyroidism or still other extraskeletal abnormalities, Arch. Path. **33**: 777–816 (June) 1942.
5. Garlock, J. H.: Differential diagnosis of hyperparathyroidism, with special reference to polyostotic fibrous dysplasia, Ann. Surg. **108**: 347–361, 1938.
6. Albright, F., Scoville, B., and Sulkowitch, H. W.: Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation, and a gonadal dysfunction, Endocrinology **22**: 411–421 (April) 1938.
7. Helfet, A. J.: A new conception of parathyroid function and its clinical application: a preliminary report on the results of treatment of general fibrocystic and allied bone disease and of rheumatoid arthritis by aluminum acetate, Brit. J. Surg. **27**: 651–677 (April) 1940.

TUBERCULOSIS OF THE LIVER AND GALL-BLADDER WITH ABSCESS FORMATION: A REVIEW AND CASE REPORT *

By S. A. Leader, M.D., *Chicago, Illinois*

Tuberculosis of the liver is known to occur in the following forms:

1. Miliary, as a part of a generalized miliary tuberculosis, or terminally, in those dying of pulmonary tuberculosis.
2. Local:
   A. Focal or nodular, consisting of single or multiple conglomerate tubercles forming tumor-like tuberculomas or abscesses.
   B. Tubular form (considered by some a variant of A), involving the intrahepatic bile ducts.[46]

While miliary tuberculosis of the liver is quite common and is said to occur in from 50 to 80 per cent [39] of all patients dying of pulmonary tuberculosis, the other forms are uncommon. However, in 1858 Bristowe [6] had already found 12 cases of solitary tubercles of the liver with cavity formation in 167 instances of tuberculous ulceration of the intestine. In 1905, Rolleston [47] classified tuberculosis of the liver into miliary and local forms in his book on diseases of the liver and gall-bladder. He cited, among others, the cases reported by Bristowe,[6] Moore,[38] Milian and Hertz,[37] von Clement,[59] and two of his own and, later, several more. In 1930, Morris [39] collected 11 cases in a survey of the literature, and added one of his own. He located only one case by sending questionnaires to several pathologists and to tuberculosis hospitals with a total bed capacity of 11,455 in various parts of this country. Since then, further cases have been reported from time to time, among them three tuberculous abscesses of the liver found by Maffei [34] in 601 autopsies on tuberculous patients. Including all of the foregoing, the writer has found a total of 80 cases.† (Geraghty [18] states that 43 cases of solitary tubercles, miliary tuberculosis and disseminated tuberculosis of various types involving the liver were found in 2,701 autopsies at the University Hospital, but did not specify how many of each; hence, his cases have been omitted from the total of 80.)

Tuberculosis of the gall-bladder is much rarer than local tuberculosis of the liver, but a case was described in 1870 by Gaucher and another by Lancereaux in 1871.[27] In 1908 Simmonds [53] collected eight cases, including two of his own. He described two types: chronic ulcerative tuberculosis of the gall-bladder, with or without gall-stones, and an acute form associated with generalized miliary tuberculosis. Comprehensive reviews of this subject have been published by Rankin and Massie [44] in 1926, Case in 1928,[8] and Lazarus in 1934,[30] each accompanied by a single case report. Since then, a number of additional cases have been reported, including one in 1949 by Elfving [13] and one in 1950 by Vallejo.[58] Elfving again reviewed the literature and noted, as previously emphasized by others, that less than half of the cases had been proved histologically. Even with all of these, there were only 37 cases.

* Received for publication June 15, 1951.
From the Department of Radiology, University of Illinois College of Medicine, Chicago.
† While an extensive survey of the literature was made in preparing this paper, the writer feels certain that he has not exhausted the field.

In only six cases where complete data were available to the writer was there involvement of both the liver and gall-bladder, and in one of these [27] the liver involvement was minimal.

The following case is presented because of its interesting radiographic findings as well as its uncommon occurrence.

Case Report

A 46 year old white male with a record of repeated hospitalizations elsewhere in the past 14 years for diabetes mellitus was first admitted on September 18, 1942, for gangrene of the left middle toe. His initial blood sugar was 242; urinary sugar

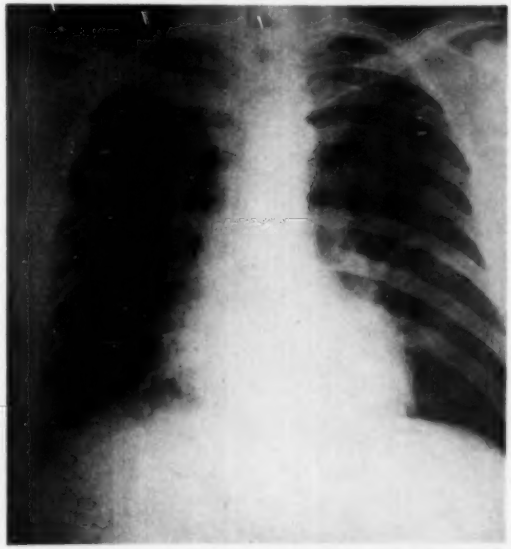


Fig. 1. November 25, 1949, bilateral pulmonary tuberculosis with cavitation, left, during final hospitalization.

was 2.5 per cent; acetone was found in the urine. A chest radiograph revealed a lesion of the right lung near the base, proved to be tuberculous by sputum examinations and guinea pig inoculations. In addition, mild hypertension (blood pressure, 170/104 mm. of Hg) and general arteriosclerosis were found. The diabetes was controlled with the aid of insulin, and the gangrene of the toe cleared up. The tuberculous process spread to the left lung, but subsequently, the pulmonary condition gradually improved. The patient gained weight, his sputum became negative, and guinea pig inoculation was also negative. He was discharged on September 13, 1945, in good condition, the tuberculosis being considered inactive (figure 1).

On October 24, 1949, he was re-admitted following an attack of unconsciousness, twitching of the left arm and leg and left side of the face the preceding night. Other symptoms elicited later were gradual weight loss for one year, especially in the past five or six months, intermittent diarrhea and constipation for one year, and attacks of

vomiting for several years. Physical examination disclosed a left hemiparesis, an enlarged, very firm liver and mild sclerosis of the retinal vessels. Blood pressure was 90/60 mm. of Hg. The patient was somewhat confused at first, but this later cleared. X-ray examination of the chest revealed a pulmonary lesion (figure 2), and sputum examinations were positive for tubercle bacilli.

The following are some of the many other laboratory studies made: Initially, blood sugar, 294; urinary sugar, 2.5 per cent; non-protein nitrogen, 36; red blood cells, 5,100,000; white blood cells, 14,300; hemoglobin, 10 gm. Subsequently, red blood cells ranged from 3,590,000 to 2,730,000, white blood cells from 9,900 to 23,000. The van den Bergh test was negative. Serum albumin, 2.6; serum globulin, 4.6; later, serum albumin, 3.8; serum globulin, 3.6. Serum amylase, 14; alkaline phos-

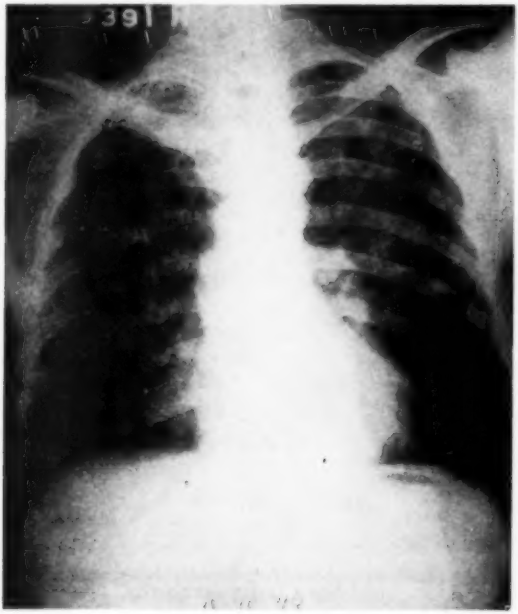


FIG. 2. June 19, 1945, just before discharge. Residual tuberculosis adjacent to left hilum.

phatase, 19.5; serum phosphorus, 4.1; serum calcium, 9.1; bromsulfalein, 15 per cent; thymol turbidity, 1 unit; urobilinogen, 1 mg. per 100 c.c. Spinal fluid examination was entirely negative, and blood Kahn was negative. Gastric analysis on November 24 revealed no free hydrochloric acid and a total acidity of 12 in the fasting state; after administration of 7 per cent ethyl alcohol and histamine, there was still no free acid; the total acidity was 20.2. On December 28 there was no free acid and a total acidity of 16 in a specimen from the fasting stomach; three hours after histamine, there was free acidity of 4 and a total of 39, but no free acid on the first three specimens.

Hospital Course: There were periods of irregular fever; one febrile episode responded to crysticillin, but fever continued to recur, the last episode beginning on

January 12, 1950, the temperature rising to 103° F. and continuing until the patient died on January 17. A gastrointestinal series on November 5, 1949 (figure 3) revealed no definite abnormality, but on reëxamination on December 30 (figure 4a) there was an extensive filling defect in the prepyloric region, with deformity of the duodenal bulb and evidence of a fistulous connection between the gall-bladder and the duodenum. This was interpreted as due to a rapidly progressive malignant lesion such as lymphosarcoma (although at a tumor board conference it was stated that an inflammatory process was quite possible). On January 8, 1950, an aspiration biopsy of the liver was done, but only necrotic cells were found. One examiner noticed

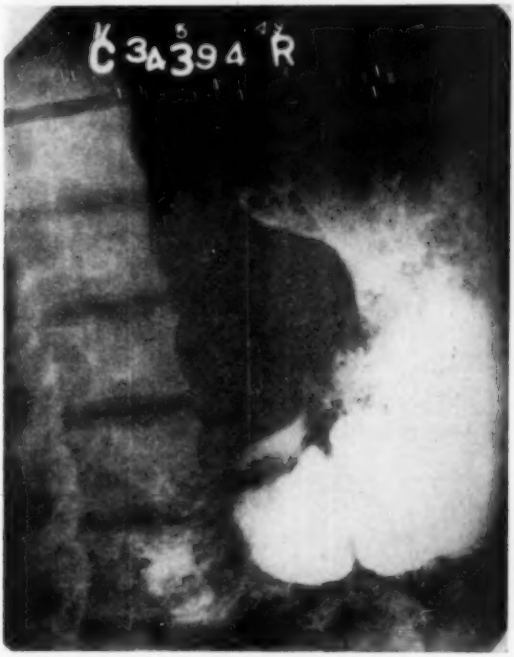


FIG. 3. November 5, 1949, stomach apparently normal.

slight jaundice, but this, if present, was quite transient, as it was not noted on admission or at autopsy. The diabetes became increasingly difficult to control. On January 11 he had symptoms of an insulin reaction, including convulsions. Following this, he required large amounts of glucose and no longer needed insulin, but became progressively weaker until his death on January 17.

At autopsy, the liver edge, the stomach and small bowel were matted together by adhesions. There were 2,000 c.c. of reddish fluid in the peritoneal sac, and multiple pinhead-sized tubercles in the peritoneum. The liver weighed 2,400 gm. and contained many fluctuant nodules, 5 mm. to 4 cm. in diameter, which, on section, were found to contain abscesses. Purulent material was also found in the biliary system. The gall-bladder was replaced by a necrotic mass of dark gray material. No com-

munication was demonstrated between the duodenum and the gall-bladder (in spite of the rather typical x-ray findings; however, death occurred 17 days after the last gastrointestinal series). No ulceration of the bowel was found. Other findings were bilateral pulmonary tuberculosis, with cavitation and caseous tuberculosis of the peribronchial and aortic lymph nodes. Microscopic examination revealed tuberculosis of the liver and gall-bladder, lymph nodes, peritoneum and lungs. There were also fatty changes in the liver. In addition, coronary sclerosis and arteriosclerosis of the kidneys were present.

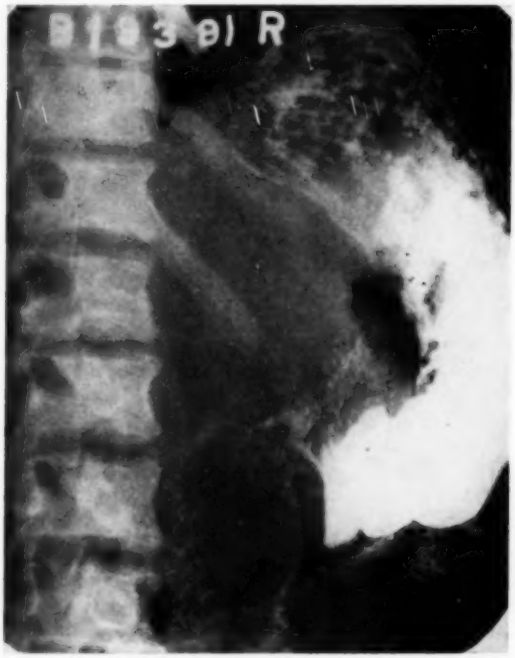


FIG. 4a. December 30, 1949, marked filling defect in prepyloric segment of stomach.

To summarize the case briefly, a diabetic developed pulmonary tuberculosis which responded to conservative treatment. Later, a left hemiparesis occurred; the pulmonary lesion flared up, the diabetes became worse, gastrointestinal symptoms became prominent and the liver enlarged considerably. At autopsy, extensive tuberculosis of the liver and gall-bladder was found, with abscesses of the liver and complete necrosis of the gall-bladder, as well as tuberculous peritonitis and caseous tuberculosis of the peribronchial and aortic lymph nodes. The x-ray findings, particularly the extensive filling defect in the prepyloric region of the stomach, with distortion of the duodenum, certainly were consistent with a diagnosis of malignancy. However, the rapid change in the appearance

of the stomach should, perhaps, have cast some doubt on this diagnosis. Buckstein [7] states that, roentgenologically, the differentiation between inflammatory and malignant lesions of the stomach may be extremely difficult and, in some cases, the significance of the deformity may be impossible to evaluate.

At this point, it would be of interest to mention briefly some of the cases reported in the literature. Lancereaux [27] also described a caseous mass replacing the gall-bladder, tuberculous granulations in the common duct and a few in the liver, and tubercles in the spleen and mesenteric nodes; however, the gall-bladder was too necrotic for microscopic study, so that no histologic proof

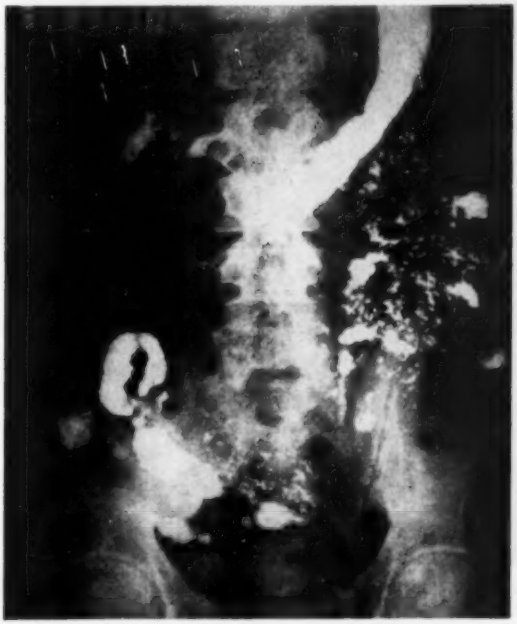


FIG. 4 b. At four hours, filling defect still shown, plus distorted duodenal bulb, barium and small gas bubbles in region of gall-bladder.

was available. Hegler [22] found tumor-like tuberculous cholecystitis and cholangitis associated with stones in the gall-bladder and common duct. Ajello's [1] case was a 2 month old infant with extensive generalized tuberculosis in which the lungs, bowel and spleen were involved, as well as the gall-bladder and liver. Walters and Church [60] cited an instance of a tuberculous mass in the liver, apparently originating from a similar lesion of the gall-bladder and associated with tuberculous peritonitis limited to the right upper quadrant of the abdomen. Psenner [43] reported a case of tuberculosis of the gall-bladder and duodenum with a fistula between these structures demonstrated by radiographic examination of the

stomach. This patient was a 74 year old woman who had gastric anacidity and an enlarged liver. Clinically, a diagnosis of tumor of the stomach was made, but autopsy revealed tuberculosis of the duodenum and gall-bladder, tuberculous ulcers of the small bowel, tubercles in the parietal peritoneum, bilateral pulmonary tuberculosis and gall-stones. Psenner postulated that the gall-bladder lesion was secondary to a tuberculous ulcer of the duodenum which had perforated into the gall-bladder, but could not exclude the possibility of tuberculous involvement of

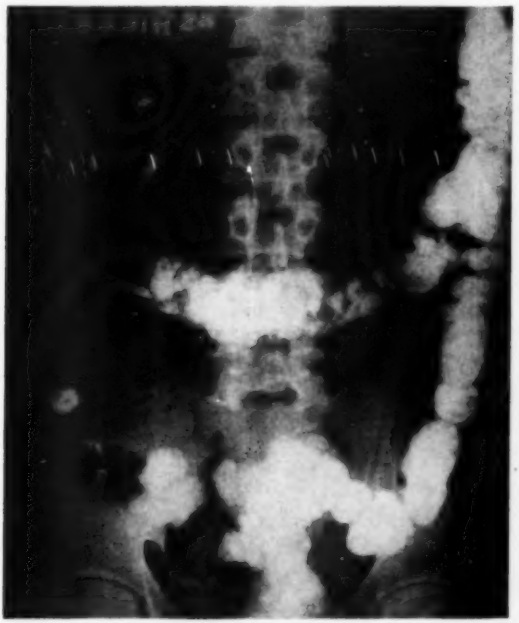


FIG. 4c. At 24 hours, still barium in region of gall-bladder, and gas bubbles clearly seen in gall-bladder.

the gall-bladder with perforation into the duodenum. That extensive tuberculosis of the gall-bladder can occur without any involvement of the duodenum is well demonstrated by our case, among others.

DISCUSSION

I. Local tuberculosis of the liver is usually diagnosed at autopsy, but occasionally at laparotomy, as emphasized in the literature. The case reported by Herrell and Simpson [23] and the one by Choremis and Ninios [10] were both discovered by laparotomy. In the first of these a large mass, containing much necrotic material and a small amount of thick pus, was found in the right lobe of the liver. The patient was closed without drainage and was considered im-

proved four months later. The patient of Choremis and Ninios was a 14 year old boy operated on for suspected liver abscess; after surgery, he was treated with streptomycin and was stated to be in good health five months later. In both instances, the diagnosis of tuberculosis was established by biopsy.

When all of the cases of local tuberculosis found in this review are studied, several points stand out:

1. The condition is said to occur most frequently in children, and in various racial groups with little natural immunity to tuberculosis, such as Negroes and Igorotes, but is by no means restricted to these groups.
2. In the vast majority of cases, tuberculosis is present elsewhere in the body, only very few instances having been recorded in which the lesion of the liver was either the only one present or the oldest tuberculous lesion. In this regard it should be mentioned that, among the other tuberculous lesions present, there were six cases of tuberculosis of one or more vertebrae.
3. The most common findings in tuberculous abscess of the liver, in order of their frequency, are fever, liver enlargement and chills. Jaundice is seldom encountered in this condition, as stressed by Geraghty and others, but has been observed by Thayer,[54] Maximowitsch,[36] Sheldon,[52] Warthin,[61] and Rosenkranz and Howard.[49]

The two principal conditions to be differentiated from local tuberculosis of the liver are liver abscess of other etiology, and malignancy. The former condition is apt to be particularly troublesome to differentiate when fever is a prominent symptom and other tuberculous lesions are not demonstrable. However, malignancy may be equally difficult to rule out; for example, Ariel [2] described a case diagnosed clinically as carcinoma of the stomach with metastasis. He cited a case of Fraenkel's in which a diagnosis could not be made at surgery, and another by Lodyschenskaja [32] where, at autopsy, sarcoma was suspected until microscopic examination revealed tuberculosis. Maximowitsch [36] had a similar experience, finding hard nodules in the liver which at surgery were considered to be typical of carcinoma but which, at necropsy, proved to be tuberculous abscesses. Benda [4] and his colleagues found tubercle bacilli in a large, encapsulated abscess of the liver in a patient with pulmonary tuberculosis. A small adenoma with a capsule identical to that of the abscess was present in a different part of the liver. Because no tubercles were found in the abscess, these authors had difficulty in explaining their findings, and suggested the adenoma might have involved a dormant tuberculous lesion and activated it. Rolleston [48] mentions a case, reported by Moore, of a tuberculous abscess of the liver associated with carcinoma of the pylorus. In our own case, the liver enlargement, the presence of a large, filling defect in the stomach on x-ray, the almost complete achlorhydria, all spoke for malignancy. Incidentally, Thayer [54] also noted achlorhydria and a markedly decreased total acidity in his patient. Among the rare conditions to be differentiated are syphilis and actinomycosis. Fischer [15] described a case which grossly appeared to be a gumma, but which on microscopic examination revealed typical tubercles and tubercle bacilli. There were other findings suggesting syphilis, but he was unable to demonstrate the

organisms. Rolleston [48] mentions a specimen in the pathological museum at Birmingham, England, which resembled actinomycosis. Winternitz [64] found a rare combination of tuberculosis of the stomach and tuberculous cavities of the liver, as well as tuberculosis of the mediastinal, bronchial and mesenteric glands and of the pleura.

II. It has been observed repeatedly that tuberculosis of the gall-bladder has no characteristic symptomatology, so that, up to the report of Vallejo [58] in 1950, the diagnosis was made only at surgery or autopsy.*

Vallejo made a tentative diagnosis of tuberculosis of the gall-bladder in a 27 year old man with pulmonary and laryngeal tuberculosis who had improved on streptomycin therapy. As the gall-bladder condition did not respond to further streptomycin, a laparotomy was done. Nodular tubercles, tuberculous ulcers and tubercle bacilli were found in the gall-bladder, and also tuberculous peritonitis.

When all of the cases of tuberculosis of the gall-bladder are analyzed, the following features are noted:

1. It occurs most commonly in women over 30; of the 38 cases, including the author's, 18 were in females, seven in males, one of these a 9 month old infant; in the remaining 13, either the sex was not stated or the author did not have access to the complete reference. One of the latter was in a two month old infant. Of the 18 cases in females, there were five from 30 to 40, six from 40 to 50, and six over 50; in one, the age was not specified.
2. Gall-stones are frequently associated with this condition. In 20 cases gall-stones were present; in nine there were no gall-stones, and in the remaining nine, either the complete reference was not accessible to the writer or no mention was made of this point.
3. Tuberculosis of the gall-bladder has been described with and without other tuberculous lesions in approximately the same proportions; however, some of the cases in which tuberculosis was not found elsewhere were only given general physical examinations, and some of the earlier cases did not have chest x-rays. This can be very misleading; for example, Gonzalez' [20] patient was a well nourished woman with symptoms referable only to the gall-bladder; it was only after tuberculosis of the gall-bladder was found at surgery that a film of the chest was made, and this revealed extensive pulmonary tuberculosis. In absence of a complete autopsy, it would certainly be difficult to establish that no other tuberculous lesion was present.
4. The most common symptom described is epigastric pain, made worse by eating.
5. The most outstanding physical sign is the presence of a tender tumor in the right hypochondrium.[30]
6. Jaundice occurs rarely.

* While the case of Lancereaux has been cited as one in which the diagnosis was made clinically, a careful check of the original report in 1871 indicates that only chronic liver disease was diagnosed. In his book in 1899, referred to by previous reviewers, Lancereaux stated that the diagnosis of tuberculosis of the gall-bladder should be considered in the presence of other tuberculous lesions in a patient with symptoms of gall-bladder colic, progressive downward febrile course, jaundice and doughy enlargement of the gall-bladder.

The most common preoperative diagnoses of cholecystitis and cholelithiasis are readily accounted for by the foregoing. However, other diagnoses are occasionally made. For example, one case was called sarcoma, two were believed to be carcinoma, one renal tumor and another, perforating duodenal ulcer with abscess (noted by Lazarus and Eisenberg [30] in their review).

In conclusion, while local tuberculosis of the liver is uncommon, the diagnosis cannot be considered entirely academic since the advent of streptomycin and other substances in the treatment of tuberculosis. When there is evidence of liver enlargement and fever, particularly in the presence of tuberculosis elsewhere in the body, local tuberculosis of the liver should be considered. Tuberculosis of the gall-bladder is even rarer and is equally difficult to diagnose, as attested by the single recorded case in which a clinical diagnosis was made. Here again, the presence of other tuberculous lesions may be helpful, particularly in women over 30 with evidence of gall-stones and a tender tumor in the right hypochondrium.

Summary

1. A review of the literature is given, including a classification of tuberculosis of the liver.

2. A case of tuberculosis of the liver and gall-bladder is described, with radiographic evidence of a fistula between the gall-bladder and duodenum and filling defect of the stomach resembling malignancy.

3. Local tuberculosis of the liver occurs most frequently in children and in such groups as Negroes and Igorots.

4. In the great majority of cases, the lesion of the liver is secondary to tuberculosis elsewhere. The vertebrae are not uncommonly involved.

5. The most common findings in tuberculous abscesses of the liver are fever, liver enlargement and chills.

6. Tuberculosis of the gall-bladder is most common in women over 30, and is frequently associated with gall-stones.

7. While tuberculosis of the gall-bladder has no characteristic symptomatology, the most common symptom is epigastric pain, made worse by eating, and the most common physical sign is a tender tumor in the right hypochondrium.

Acknowledgment

The writer wishes to acknowledge his appreciation to Mrs. Lorene Jorgensen, for her careful preparation of the manuscript; to Dr. Max Ramirez de Arellano, for translating Spanish and Portuguese references, and to Mr. Peter Lund, for preparing the illustrations.

BIBLIOGRAPHY

1. Ajello, L.: Contributo allo studio della tubercolosi della cistifellea, Pathologica **20**: 599, 1928.
2. Ariel, M. B.: Zur Frage der Knotigen, sogenannter—"Abscedierenden" Tuberkulose der Leber, Virchows Arch. f. path. Anat. **279**: 137, 1930.
3. Ashton, N.: Multiple tuberculomata of the liver with case report, J. Path. and Bact. **58**: 95–97, 1946.
4. Benda, R., Gauthier-Villars, P., and Goulfier, F.: Large caverne tuberculeuse du foie ou adenome hepatique necrose chez un tuberculeux, Bull. et mém. Soc. med. d. hôp. de Paris **56**: 449–453, 1940.

5. Blair, E. J., and Pagel, W.: Fulminant tuberculous septicemia and other atypical forms of abdominal tuberculosis, Tubercle **28**: 115–123, 1947.
6. Bristowe, J. S., cited by Geraghty.[18]
7. Buckstein, J.: The digestive tract in roentgenology, 1948, J. B. Lippincott Co., Philadelphia, pp. 254–255.
8. Case, J. T.: Tuberculosis of the gall bladder, Bull. Battle Creek San. and Hosp. **23**: 71–82, 1928.
9. Case, J. T., and Warthin, R. S.: Tuberculosis of the gall bladder with report of a case and a note on the management of duodenal fistula, Tr. West. S. A. **35**: 171, 1925.
10. Choremis, C. V., and Ninios, N.: A case of tuberculous hepatitis and its biological reactions, Acta paediat. **37**: 188–194, 1949.
11. DeCrespigny, C. T., and Cleland, J. B.: A case of primary multiple tuberculoma of the liver with a degenerated hydatid cyst, M. J. Australia **1**: 151, 1923.
12. Delitala, P.: Contributo alla conoscenza della tubercolosi della cistifellea, Studi sassar **2**: 209, 1931.
13. Elfving, G.: Tuberculosis of the gall bladder, Ann. chir. et gynaec. Fenniae **38**: 80, 1949.
14. Ernst, K.: Isolierte konglomerat Tuberkel der Leber, 1901–1902, Path. Gesellschaft, Hamburg, cited by Fischer.[15]
15. Fischer, W.: Uber groszknotige tumorahnliche Tuberkulose der Leber, wahrscheinlich kombiniert mit Syphilis, Virchows Arch. f. path. Anat. **188**: 21, 1907.
16. Fletcher, H. M.: Tuberculous cavities of the liver, Tr. Path. Soc. London **50**: 160, 1899, quoted by Morris.[39]
17. Frank, L.: Primary tuberculosis of the liver, Am. J. M. Sc. **123**: 630, 1902.
18. Geraghty, F. J.: Jaundice in tuberculosis, Am. Rev. Tuberc. **45**: 521–527, 1942.
19. Goni-Moreno, L.: Ulcer gastrica-tuberculosis hepatica, Bol. y trab., Acad. argent. de cir. **28**: 1207–1210, 1944.
20. Gonzalez, G. R.: Tuberculosis de la vesicula biliar, Rev. méd. de Chile **71**: 694–696, 1943.
21. Gravier, L., and Puig, R.: A case of primary tuberculosis of the spleen and liver, Lyon méd. **143**: 107–112, 1929.
22. Hegler, C.: Tumorartige Cholecystitis und Cholangitis tuberkulosa, Virchows Arch. f. path. Anat. **254**: 272, 1925.
23. Herrell, W. E., and Simpson, W. C.: Recurrent hyperpyrexia due to solitary tuberculoma of the liver, J. A. M. A. **111**: 517, 1938.
24. Izzo, R. A., Ferras, J. B., and LaPlace, J. M.: Tuberculosis de vesicula biliar, Rev. Asoc. méd. argent. **51**: 27–29, 1937.
25. Kaiser, S.: Abcesso, tuberculosa do figado, Rev. brasil. med. **2**: 662–666, 1945.
26. Kjolhede, K. T.: Cholecystitis tuberculosa, Nord. med. **39**: 1292, 1948, cited by Elfving.[13]
27. Lancereaux, E.: Atlas d'anatomie pathologique, 1871, Victor Masson et Fils, Paris, p. 70.
28. Lancereaux, E.: Traite des maladies du foie et du pancreas, 1899, Doin, Paris, pp. 661–663.
29. Lauber, H. J., and Schulte, F. H.: Beitrag zum Krankheitsbild der Cholecystitis tuberkulosa, Zentralbl. f. Chir. **66**: 1490, 1939.
30. Lazarus, J. A., and Eisenberg, A. A.: Tuberculosis of the gall bladder, report of a case of primary tuberculous cholecystitis, Am. J. Surg. **24**: 166–173, 1934.
31. Levrat, M., and Ballivet, J.: Thermic inversion during five months as a symptom of caseous tuberculosis of the liver, Lyon méd. **163**: 246–250, 1939.
32. Lodyschenskaja-Gazencer-Trudy: ob-wa, Patologow, St. Petersburgh: 112, 1911, cited by Ariel.[2]
33. Macaigne and Finet: Tuberculosis of the liver, diffuse nodular hepatitis, Bull. Soc. anat. de Paris **49**: 354, 1894, cited by Morris.[39]

34. Maffei, W. E.: Tuberculose cavernosa da figazo, An. Fac. de med. da Univ. de São Paulo **180**: 411–422, 1937.
35. Mallory, T., Castleman, B., and Towne, V.: Case No. 37011, Weekly Clin. Path. Exercises, Mass. Gen. Hosp., New England J. Med. **244**: 22–26, 1951.
36. Maximowitsch, A. S.: On "primary" multiple tuberculous abscesses of the liver, Zentralbl. f. d. ges. Chir. u. Grenzgeb. **54**: 2292, 1927.
37. Milian, G., and Hertz, J.: Granulie hepatosplenique, Bull. Soc. anat. de Paris **75**: 53, 1900.
38. Moore, F. C.: Med. Chron. Manchester **2**: 5, 1899.
39. Morris, E.: Tuberculosis of the liver, Am. Rev. Tuberc. **22**: 585–592, 1930.
40. Mottura, G.: Sopra un caso di tubercolosi ulcerosa della colociste, Gior. Accad. med. Torino **105**: 70, 1942, Abstracted in Zentralbl. org. f. ges. Chir. **107**: 709, 1943.
41. Pagel, W.: Lung lesion in extrapulmonary tuberculosis; morbid anatomical aspects, Papworth Research Bull. **2**: 57, 1938, Quoted by Ashton.[3]
42. Piergossi, A.: Fistola biliare interna associata a fistola digiunocolica in soggetto con peritonite tubercolare, Arch. radiol. **16**: 549, 1940, abstracted in Zentralbl. org. f. ges. Chir. **105**: 249, 1942.
43. Psenner, L.: Uber eine tuberkulose Gallenblaseduodenalfistel, Wien. klin. Wchnschr. **1**: 46, 1941.
44. Rankin, F. W., and Massie, F. M.: Primary tuberculosis of the gall bladder, Ann. Surg. **83**: 800–806, 1926.
45. Rapant, V.: Gallenblasetuberkulose, Časop. lék. česk. **2**: 1499, 1931, abstracted in Zentralbl. org. f. ges. Chir. **58**: 177, 1932.
46. Robinson, L. F.: Report of case of large solitary tuberculous abscess of liver, U. S. Nav. M. Bull. **20**: 721, 1924.
47. Rolleston, H. D.: Diseases of the liver, gall bladder and bile ducts, 1905, Macmillan and Co., London, p. 336.
48. Rolleston, H. D., and McNee, J. W.: Diseases of the liver, gall bladder and bile ducts, 3rd Ed., 1929, Macmillan and Co., London, p. 379.
49. Rosenkranz, K., and Howard, L. D.: Tuberculosis of the intrahepatic bile ducts, Arch. Path. **22**: 743, 1936.
50. Sasano, K. T., and Medlar, E. M.: Tubercle bacilli in the bile, Am. Rev. Tuberc. **10**: 392, 1924.
51. Sergent, E.: Tubercules et cavernes biliaires; recherches anatomopathologiques, bacteriologiques et experimentales; pathogenie de la tuberculose de voies biliaires, Thèse de Paris **94**: 164, 1895.
52. Sheldon, W. P. H.: Massive tuberculosis of the liver, Tubercle **5**: 1343, 1927.
53. Simmonds, M.: Ueber Gallenblasentuberkulose, Centralbl. f. allg. Path. u. path. Anat. **19**: 225–226, 1908.
54. Thayer, W. S.: On disseminated caseating tuberculosis of the liver, Bull. Johns Hopkins Hosp. **22**: 146–149, 1911.
55. Torrey, R. G.: The occurrence of miliary tuberculosis of the liver in the course of pulmonary tuberculosis, Am. J. M. Sc. **151**: 549, 1916.
56. Ullom, J. T.: The liver in tuberculosis, Am. J. M. Sc. **137**: 694, 1909.
57. Urin, A. G., and Kostenko, P. G.: Cavernous tuberculosis of the liver, Problemy tuberkuleza, Tsent. tub. int. NKZ drava-yauzskiy b 9 Moskva **9–10**: 67–72, 1939.
58. Vallejo, E. A.: Acute tuberculous cholecystitis, Gastroenterology **16**: 501–504, 1950.
59. Von Clement, G.: Ueber seltener Arten der Combination von Krebs und Tuberkulose; Magenkrebs mit groszknotiger Leber tuberkulose, Virchows Arch. f. path. Anat. **139**: 35, 1895.
60. Walters, W., and Church, G. T.: Primary tuberculosis of the gall bladder, Minnesota Med. **17**: 580–582, 1934.

61. Warthin, A. S.: Acute pylephlebogenous tuberculosis of the liver with clinical picture of acute infectious jaundice, Trans. 4th Annual Meeting, National Assoc. for Study of Prevention of Tuberculosis, 1928.
62. Warthin, A. S.: The occurrence of icterus in tuberculosis, Internat. Clin. **1**: 89, 1911.
63. Wethered, F.: Tubercular excavation of the liver, Tr. Path. Soc. London **40**: 139, 1888–1889.
64. Winternitz, M.: Tuberculosis of the stomach; tuberculous cavities of the liver with report of a case, Bull. Johns Hopkins Hosp. **19**: 223, 1908.

PERIARTERITIS NODOSA: REPORT OF A CASE TREATED WITH PARA-AMINOBENZOIC ACID *

By Thomas J. McGurl, Jr., M.D., *New York, N. Y.*

Periarteritis nodosa continues to be a disease of unknown etiology with protean manifestations for which there is no known specific therapy. Many causes of this disease have been postulated, including sensitization to serums, drugs, infections, etc. However, no factor common to all cases has been found.[1, 2] It is characterized by an inflammatory, necrotizing reaction in the walls of small arteries and arterioles, the earliest stage of which consists of a period of hyaline degeneration of the media. This is followed by infiltration of the coats with polymorphonuclears, eosinophils, lymphocytes and plasma cells. Later there is fibroblastic proliferation, with partial or total occlusion of the lumen. Aneurysmal dilatation of the vessel may produce nodule formation along the course of the arteries, and there may be thrombosis and hemorrhage.

Some of the most common signs and symptoms are fever, leukocytosis, albuminuria, abdominal pain, hypertension, edema, neuritis, hematuria, weakness, weight loss, etc. Striking cachexia and emaciation may develop if the illness is prolonged. Eosinophilia is often found if a sufficient number of smears are examined. The sedimentation rate is usually elevated, and anemia is commonly present. Hematuria and albuminuria are frequent. When there is involvement of the coronary arteries, electrocardiographic changes are found. The positive diagnosis, of course, depends on a study of the pathologic lesion.

The duration of the disease is usually a matter of months, but it may last for years. It may be punctuated by periods of remission and relapse. Recovery is said to take place in 5 to 10 per cent of the cases.

Logue and Mullins [3] quote Klemperer's [6] comment on the relationship of periarteritis to other collagen diseases. Because of this assumed relationship, and because of the fact that Zarafonetis [7] has reported beneficial effects in certain collagen diseases treated with para-aminobenzoic acid, we have treated one proved case of periarteritis nodosa with this drug. Since our patient is alive and well after 15 months, and since the course of the disease seemed to be influenced by para-aminobenzoic acid, we thought it of interest to report the case.

* Received for publication March 21, 1951.
From Medical Service, Veterans Administration Hospital, Providence, R. I.
Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Case Report

The patient, a 50 year old white male, was admitted to the Veterans Administration Hospital in Providence, Rhode Island, on July 11, 1949. He had been perfectly well until three weeks before admission, when he began to notice a sensation of pressure beneath his sternum which was not affected by swallowing, breathing, motion, etc. He had some inclination to clear his throat, but no cough. For two weeks prior to admission he had found his temperature to be ranging between 99° F. and 102.6° F. Two weeks before admission he consulted his family physician, who gave him some form of sulfonamide drug which he took up until the day before admission. Shortly after starting this drug he noticed abdominal distress with crampy pains in his abdomen which lasted day and night continuously. He occasionally had low back pain, mostly on the right side. Three days prior to admission he was given 300,000 units of procaine penicillin. Neither drug had any effect on his fever.

Admission to Hospital: His chief complaint was fever and a sensation of pressure beneath his sternum. His past medical history was noncontributory. The gallbladder and appendix had been removed in 1938. He was told that his blood pressure was elevated at the beginning of this illness.

Physical Examination on admission revealed an obese white male who was well developed and nourished and not severely ill. Many fine moist râles were heard at both lung bases. His blood pressure was 136/85 mm. of Hg. Cardiovascular examination was normal. There was no lymphadenopathy. The remainder of the examination was completely negative.

Laboratory Work: The initial urinalysis showed a 1 plus albumin and 10 red blood cells with 3 white blood cells per high power field. Agglutinations for the usual infectious diseases, repeated many times throughout his stay, were all negative. Initial blood count on admission was normal, except for an eosinophil count of 21 per cent. Blood Kahn test was negative. The sedimentation rate was 49 mm. per hour. Blood urea nitrogen shortly after admission was 43 mg. per cent. Urine cultures did not reveal any pathogenic organisms. Examination and culture of his stools were normal. Several electrocardiograms taken throughout his hospital stay were within normal limits. Initial x-ray of his chest was negative. A gastrointestinal series was normal. An intravenous pyelogram on July 19 demonstrated slightly impaired concentrating power of both kidneys; there was a bifid pelvis on the right, but no obstruction on either side. Barium enema revealed fixation of the midsigmoid, thought to be due to an adhesion. On August 5 an x-ray of the chest revealed the left diaphragm to be elevated and not quite so sharply defined as previously. About 2 cm. above the diaphragm a horizontal shadow which gave the appearance of a disk-like atelectasis crossed the lung field. Repeat x-ray on September 7 showed some improvement in this condition. X-ray of the chest on November 30 showed the lung fields to be clear. Trichinella skin test was negative in 24 and 48 hours.

Course in Hospital: Toward the end of the first week of hospitalization the patient complained of soreness in his testicles, which appeared during the evening and had disappeared by morning. He also complained of right shoulder pain, and soreness of left heel and one knee. There were distinct erythema and swelling about the knee joint on examination the following morning. During this period his temperature had varied between normal and 101° F. A few days later he developed numbness of the left leg, which disappeared within a few hours. Testicular pain recurred and lasted one day. Examination revealed nothing.

A biopsy of the left gastrocnemius was performed on July 27, but nothing diagnostic was found on microscopic examination. At about this time he developed ecchymotic areas about his ankles and over his buttocks. A tourniquet test was nega-

tive. His fever continued and his condition became generally worse. During the month of July the hemoglobin level dropped from 12.2 gm. to 10.8 gm. His red blood count showed a slight drop, to approximately 4,500,000 cells. During this period his eosinophil count rose to a high of 50 per cent. He then began to complain of generalized abdominal pain, which was recurrent and cramp-like in character. He developed partial paralysis of both lower legs, with diminished sensations to pin prick.

Since Zarafonetis [7] had found that para-aminobenzoic acid was of some value in such diseases as scleroderma and lupus erythematosus, it was decided to treat this patient with the drug in the hope of benefiting him. He was started on 4 gm. daily on August 9, and during the course of eight days the dosage was gradually increased to 20 gm. daily. This dose was continued until September 12, when the patient was

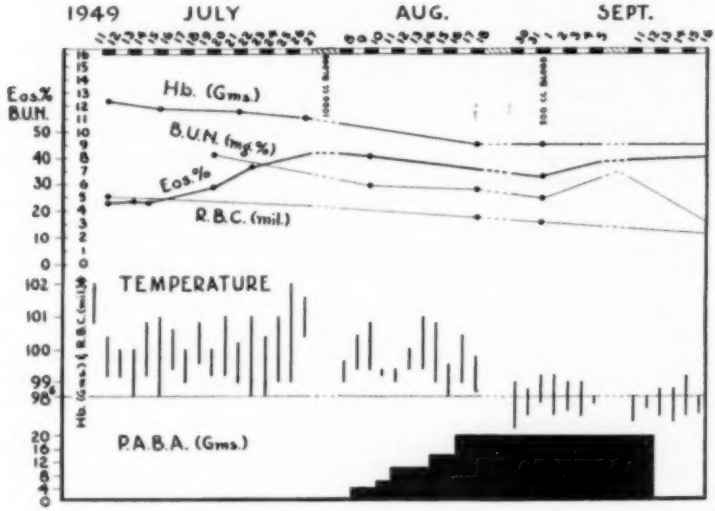


FIG. 1.

noted to be developing ankle edema. It was thought that this might be due to the retention of sodium. Most of his symptoms had subsided by mid-September, except for the parethesias and weakness of his feet. For these reasons the para-aminobenzoic acid was discontinued. On several occasions during his illness he developed soft, nontender cutaneous and subcutaneous nodules over his elbows, in the scalp and on the dorsum of the hands. These varied in size from 0.5 to 1.5 cm. in diameter. They disappeared in a matter of a few days, with the exception of one which persisted over his left elbow. This and a nodule in the right upper quadrant of his abdomen were removed and again were not diagnostic on histologic examination. However, a biopsy from his left triceps muscle was reported on September 24 as showing periarteritis nodosa.

Before starting para-aminobenzoic acid it was felt that the patient's condition, generally speaking, was perhaps a little better. However, his temperature continued

to range between normal and 101° F., with an occasional excursion to 102°. His red count continued to drop, and at the time the drug was first administered it was about 4,000,000 and the hemoglobin was 9 gm. His blood urea nitrogen ranged around 30 mg. per cent and the eosinophil count was up to 49 per cent. Between August 9 and September 1 (figure 1) his temperature curve showed a gradual decline, and after September 1 it remained normal. However, the blood urea nitrogen continued to be elevated and his eosinophil count did not drop. His red count showed a steady decline until it reached 3,500,000. It was at this point that the drug was stopped. His temperature remained normal until September 28, when it rose to 102°. For the following 10 days it ranged between normal and 100.6°. During this period his eosinophilia continued to decrease but still was abnormally elevated. His blood

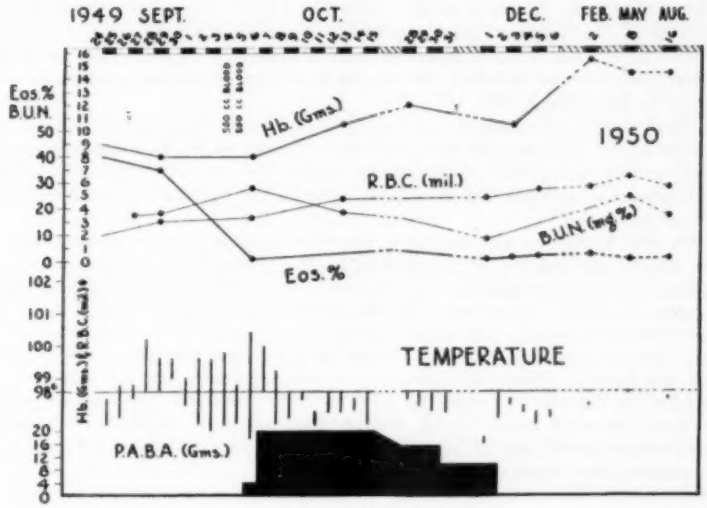


FIG. 2.

urea nitrogen continued to be elevated and his hemoglobin and red blood count remained unchanged. On October 6, because of the return of fever, para-aminobenzoic acid was again administered. At this time he had no symptoms except paresthesias and weakness of his feet. There were no objective findings except recurrent ecchymoses about his ankles. After the small initial dose, the dosage was promptly increased to 20 gm. daily; this was continued until October 27 (figure 2). On the fourth day after starting the drug, his temperature dropped to normal and remained at that level thereafter, with the exception of a few excursions to 99°. He had had a transfusion of 1,000 c.c. of blood just before resuming the administration of the para-aminobenzoic acid. The hemoglobin level rose to 10 gm. and thereafter showed a steady rise. Blood urea nitrogen showed a slow decline, as did the eosinophilia. Para-aminobenzoic acid, 20 gm. daily, was continued until October 27; thereafter it was slowly reduced until it was finally discontinued on December 1.

The patient was at home on leave of absence from November 5 to December 1, 1949. During that period he had been asymptomatic, except for the fact that he noticed very slight weakness and mild paresthesias of his feet. The ecchymoses had disappeared. During the week that he remained in the hospital, after returning from leave, his temperature remained normal. On December 1 his red blood count was 5,120,000; hemoglobin, 14 gm.; white blood cells 5,600; neutrophils, 34; lymphocytes, 58; monocytes, 6, and eosinophils, 2. His urine continued to show 2 plus albumin, and the sediment contained 40 red blood cells per high power field on one occasion, 15 on another and 5 on another; the specific gravity was 1.022. Sedimentation rate was 33 mm. per hour. Blood urea nitrogen had dropped to 8 mg. per cent. Total serum protein was 6.9 gm., with 2.5 gm. of albumin and 4.4 gm. of globulin. Liver function tests had remained normal throughout his stay in the hospital.

During the patient's leave he had taken his temperature daily, and he stated that there were about 20 elevations to 99°. After his return to the hospital no elevations were noted. Physical examination at this time was entirely negative, except for mild pallor of the skin and evidence of loss of about 20 pounds in weight. There was mild subjective weakness of both feet. It was felt he had recovered sufficiently to be discharged on December 7, 1949.

The following information regarding his course following discharge is available. On February 2, 1950, he had no complaints except for slight fatigue and weakness of his legs. At that time his sedimentation rate was 18; he had a completely normal blood count, and his urine showed a 2 plus albumin and contained 15 red blood cells per high power field.

On May 8, 1950, he was reported to have been working steadily for the preceding three months, and had few or no complaints. The weakness and paresthesias of the feet had completely disappeared. At this time a small, pea-sized subcutaneous nodule was noted in the right upper arm. His blood pressure was 182/120 mm. of Hg. His urine continued to show 2 plus albumin, with 12 red blood cells per high power field, and 2 granular casts in each field. Blood urea nitrogen was 36; complete blood count was normal; sedimentation rate was 16 mm. per hour. The last report of his condition was received on August 15, 1950, at which time his weight remained about the same; the small nodule on his arm persisted and was nonpainful. His blood pressure was 140/88 mm. of Hg. Blood urea nitrogen was 19 mg. per cent, and his complete blood count was normal.

COMMENT

We have presented a case of periarteritis nodosa proved by biopsy. The patient was treated with a drug not heretofore used in this disease, as far as we can determine from reported cases in the literature. It is well known that spontaneous recovery takes place in 5 to 10 per cent of cases of periarteritis nodosa. Review of our patient's record suggests that para-aminobenzoic acid altered the course of the disease, particularly during the second course of treatment, when the temperature on the fourth day again returned to normal and remained there with few exceptions thereafter. At the same time a gradual improvement in his general condition occurred, and hemogram and blood urea nitrogen returned to normal. The improvement continued after the drug was discontinued and the patient had returned home. It would be interesting to observe the effect of treatment with para-aminobenzoic acid in other cases of periarteritis nodosa for which, so far, there is no completely satisfactory treatment.

Summary

1. A proved case of periarteritis nodosa with remission is reported.
2. The effect of treatment with para-aminobenzoic acid is described.
3. The available evidence suggests that this drug influenced the course of the disease in a favorable manner.

Addendum

In September 1951 this patient was admitted to the hospital for allergy studies because he had developed signs and symptoms of bronchial asthma a month previously. He was told that he was allergic to sulfonamides, barbiturates, morphine, aspirin, isuprel, bananas, yams and peas.

On January 2, 1952, he was re-admitted to the Providence Veterans Administration Hospital with the chief complaint of chronic recurrent asthmatic attacks and weakness in his legs. The examination was not remarkable except for dyspnea and scattered musical râles throughout his chest. Urinalysis revealed 2 to 4 plus albumin, many hyaline and granular casts and 10 red blood cells per high power field. Eosinophils were 35 per cent of the total white count. Blood urea nitrogen was normal.

He was treated with aminophyllin and potassium iodide with good results. His temperature remained normal, except for one occasion when it was elevated to 102 degrees. This was thought to be due to a transitory pneumonitis and responded promptly to treatment.

Stock vaccine therapy was advised, and after the second weekly injection on February 12, he complained of malaise, testicular pain, and developed nodules on his forearms and both lower legs. Albumin, red blood cells and casts were increased in his urine. The vaccine was discontinued. On February 15 the patient was started on 15 gm. of para-aminobenzoic acid daily. This was continued until March 6. On February 18, ACTH, 20 mg. intravenously, was started and continued until March 9.

The nodules disappeared in three days and the patient made a marked general improvement. On March 5 he developed a generalized papular rash, which gradually disappeared without specific therapy. He was discharged from the hospital on March 26, 1952. At that time his urine showed an occasional white blood cell and casts with a trace of albumin. Eosinophils were 13 per cent of his normal total white count.

BIBLIOGRAPHY

1. Logue, R. B., and Mullins, F.: Polyarteritis nodosa; report of 11 cases with review of recent literature, Ann. Int. Med. **24**: 11–26 (Jan.) 1946.
2. Miller, H. G., and Daley, R.: Clinical aspects of polyarteritis nodosa, Quart. J. Med. **15**: 255–283 (Oct.) 1946.
3. Rich, A. R.: The role of hypersensitivity in periarteritis nodosa as indicated by seven cases developing during serum sickness and sulfonamide therapy, Bull. Johns Hopkins Hosp. **71**: 123, 1942.
4. Rich, A. R.: Additional evidence of the role of hypersensitivity in the etiology of periarteritis nodosa, Bull. Johns Hopkins Hosp. **71**: 375, 1942.
5. Rich, A. R., and Gregory, J. E.: The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity, Bull. Johns Hopkins Hosp. **72**: 65, 1943.
6. Klemperer, P., Pollack, A. D., and Baehr, G.: Diffuse collagen disease; acute disseminated lupus erythematosus and diffuse scleroderma, J. A. M. A. **119**: 331–332 (May 23) 1942.
7. Zarafonetis, J. D.: Therapeutic possibilities of para-aminobenzoic acid, Ann. Int. Med. **30**: 1188–1212 (June) 1949.

RIGHT-SIDED ENDOCARDITIS ON A PATENT FORAMEN OVALE ASSOCIATED WITH PERIARTERITIS NODOSA *

By IRVIN SUSSMAN, M.D., *Bridgeton, New Jersey*, and PRESTON PRICE, M.D., *Jersey City, New Jersey*

SUBACUTE bacterial endocarditis commonly involves either the mitral or the aortic valve. In less than 4 per cent of cases,[1] usually when the disease occurs in childhood, vegetations may be present only within the right chambers of the heart on such sites as the tricuspid valve, pulmonary valve, interventricular septal defect or patent ductus arteriosus. It has been rather striking that the most common heart anomaly, the persistently patent foramen ovale, has only once been previously described as the site of bacterial endocarditis.[2] The following patient presented the clinical features of right sided subacute bacterial endocarditis. A postmortem blood culture from the right auricle yielded *Streptococcus viridans*, and vegetations were found on the right auricular margins of the patent foramen ovale. Histologically typical periarteritis nodosa was, however, the most striking postmortem finding.

CASE REPORT

A 12 year old school girl was admitted on April 7, 1947, complaining of painful swollen ankles and fever of three weeks' duration. Except for an uneventful extraction of an abscessed tooth six weeks previously, she had been in good health until three weeks before admission, when she complained of a sore throat and running nose. These symptoms subsided after three days of bed-rest, but were followed by pain, tenderness and swelling of both ankles and the right knee, together with a slight fever. On continued bed-rest the joint symptoms subsided after several days. One week before admission the child again noted tenderness of the ankles, right knee, left wrist and left elbow. Two days later recurrent epistaxis appeared. Three days before admission there were nausea and vomiting, and on the day before admission the temperature was found to be 102° F.

At four years of age the child had had painful swollen ankles which required one month of bed-rest. At six years of age she had had scarlet fever. The family history was noncontributory.

Physical examination on admission revealed a well developed and well nourished pale, quiet young girl with a warm dry skin. The temperature was 101° F., the pulse 120, the respirations 20 and the blood pressure 130/88 mm. of Hg. The eyes, ears and nose were normal. There was marked dental caries; the tongue was coated and the pharynx was normal. There was no lymphadenopathy, and the thyroid was not felt. The chest was clear to percussion and auscultation. The heart was not enlarged; the rhythm was regular, P_2 equaled A_2, and there was a soft blowing pulmonic systolic murmur. Abdominal examination was negative, and the extremities and joints were normal.

Laboratory studies revealed a hemoglobin of 12 gm. per cent, red blood cell count of 4,000,000 and a white blood cell count of 16,000, with 86 per cent polymorphonuclears, 2 per cent eosinophils and 12 per cent lymphocytes. The platelets were 200,000 and the reticulocytes 0.6 per cent. The blood non-protein nitrogen was 32 mg. per cent and the blood sugar was 100 mg. per cent. The urine had an acid reaction, specific

* Received for publication May 11, 1951.
From the Departments of Medicine and Pathology, Jersey City Medical Center.

gravity 1.016, 1 plus albumin and negative sugar; microscopic examination showed 10 to 15 red blood cells and 2 white blood cells per high power field. Blood cultures were sterile and various agglutination tests were negative. A chest film and an electrocardiogram were normal.

During her entire 11 week hospital course the patient had a persistent fever, spiking to 102 and 103° F. despite two four-day trials of penicillin in dosages of 50,000 units every three hours. Neither a palpable spleen nor petechiae were ever noted, and 14 blood cultures were sterile. An anemia varying between 3,400,000 and 2,400,000 red blood cells, and leukocytosis varying between 10,000 and 31,000 white blood cells, were noted on six subsequent blood counts. Weekly urines persistently showed a 1 plus albumin and 5 to 10 red blood cells per high power field. The uncorrected sedimentation rate remained 35 mm. per hour.

During her eighth hospital week the blood pressure was found repeatedly elevated to 142/114 mm. of Hg. Streptomycin, 0.5 gm. every four hours, given between June 13 and June 19, reduced the fever to 100.6° F. for only the first two days, after which it remained at 103.0° F. By the tenth hospital week, on June 17, the patient became

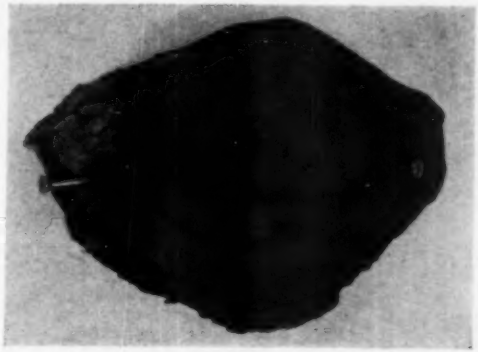


FIG. 1. Fossa ovalis of the right auricle with tiny friable vegetations.

dyspneic, a diastolic gallop rhythm was present, the liver was enlarged and tender, and a chest film revealed pulmonary congestion of the hilar regions. At this time maximal urine concentration was 1.011 and the serum albumin was 3.0 gm. per cent, the serum globulin 2.8 gm. per cent and the red blood count 2,400,000. The arm-to-tongue circulation time (saccharin) was 10 seconds, the arm-to-lung time (ether) 5 seconds; the venous pressure was 120 mm. of water. Digitalization afforded subjective improvement, the liver became normal in size, and the blood pressure was 132/102 mm. of Hg. On June 20, during her eleventh hospital week, she suddenly complained of a sharp pain in the left flank radiating to the left shoulder; gross hematuria was present and the blood non-protein nitrogen was 45 mg. per cent. She became comatose and died the following day.

Postmortem examination, restricted to the body, was done four hours after death. The skin was pale and there were no petechiae or palpable lymph nodes. Each pleural cavity contained 10 c.c. of clear straw-colored fluid, the pericardial cavity 120 c.c. and the peritoneal cavity 150 c.c. of similar clear fluid.

The *heart* weighed 250 gm. The epicardium was smooth and the myocardium firm and reddish brown. The valvular orifices were smooth and of average circum-

ferences. There was a patent foramen ovale, 1.3 cm. in diameter, with an adequate overlap of margins to permit a functional closure. On the right auricular border or limbus of the foramen ovale were noted several small pink vegetations measuring 1.0 mm. in diameter (figure 1). The coronary ostia and the coronary arteries were patent. In microscopic sections of the opposing surfaces of the right auricular margins of the foramen ovale, each endocardial surface was covered with organizing deposits of fibrin within which were occasional polymorphonuclear leukocytes. The subendocardial tissue was markedly widened and composed of fibrous tissue supporting dilated capillaries, lymphocytes and plasma cells (figure 2). The myocardium of the

FIG. 2. Low power view of a vegetation, showing organization and subendothelial inflammation.

left ventricle showed rare small foci of polymorphonuclear neutrophils and monocytes (figure 3).

Each of the *lungs* weighed 400 gm. and was grossly normal. Microscopic sections revealed a moderate amount of edema fluid in the alveoli of the lower lobes. The *spleen* weighed 340 gm. Over its upper pole was an 8.0 cm. purple, firm, elevated area which was homogeneously deep red on cut section. Microscopically this represented a large peripheral area of hemorrhage and necrosis. The intact parenchyma was essentially normal, with a moderate degree of extramedullary hematopoiesis. The *liver* weighed 1,600 gm. and was grossly and microscopically normal. The right and left *kidneys* each weighed 210 gm. The capsules stripped easily and the surfaces

were pale reddish brown and finely granular, with tiny red depressed areas. The cut surfaces were pale reddish brown, with preservation of the normal architecture. Microscopic sections of each kidney were similar and presented many medium sized arteries, with diffuse acidophilic acellular necrosis and dense polymorphonuclear infiltration of the wall. Many glomeruli had polymorphonuclear infiltration of a portion of the tuft, and rarely capsular adhesions were present. Scattered tubules contained red cells and polymorphonuclear leukocytes.

Sections of a *suprarenal gland* and of a *lymph node* showed similar acute acidophilic necrosis and polymorphonuclear infiltration of small arteries within the capsules (figure 4). The hilus of the *ovary* also contained similar acute arteritis.

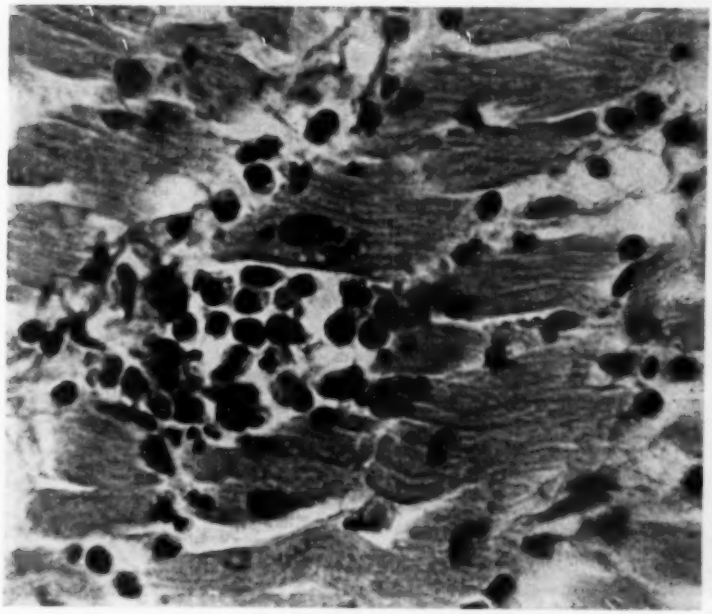


FIG. 3. High power view of left ventricle, showing focal myocarditis as seen in periarteritis nodosa.

A postmortem blood culture taken from the right auricle yielded a pure culture of *Streptococcus viridans*.

The final anatomic diagnoses were subacute bacterial endocarditis on a patent foramen ovale, periarteritis nodosa and infarct of the spleen.

DISCUSSION

It is well known that an anatomically patent foramen ovale may be demonstrated in 12 to 33 per cent of routine postmortem examinations.[3] When the opening is greater than 1.0 cm. and is of clinical significance, the term "interatrial

septal defect" is often used. Many excellent reviews [1, 3, 4, 5, 6] of the latter lesion have failed to report any instance of endocarditis on the defect itself. In 1938 Jacobius and Moore [2] presented their experience in congenital heart disease and included "one case of patent foramen ovale and subacute bacterial endocarditis of the limbus of the fossa ovalis and of the mitral valve." They felt that the congenital anomaly was of etiologic significance in causing the endocarditis. In the case we have reported, the subacute bacterial endocarditis was limited to the limbus of the fossa ovalis without other valvular disease, and no anatomic evidence of rheumatic heart disease was found.

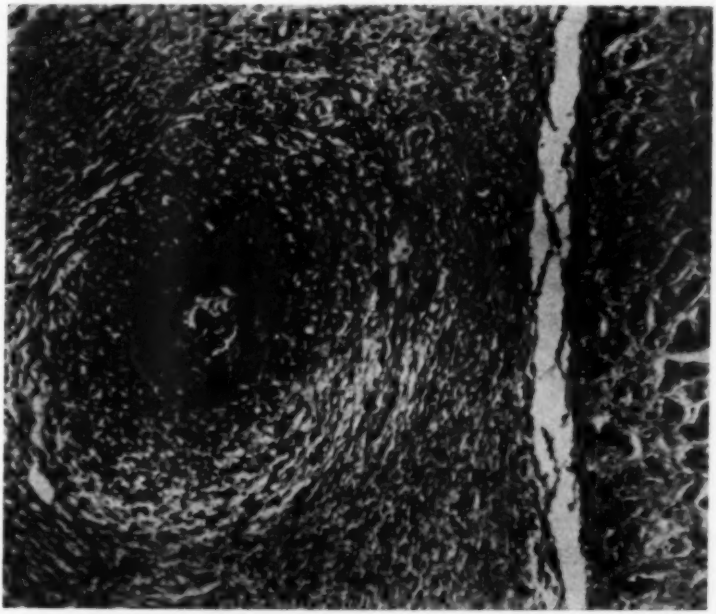


FIG. 4. Low power view of the suprarenal capsule, with typical periarteritis nodosa.

The association of periarteritis nodosa with subacute bacterial endocarditis is rather unusual, although it has occasionally appeared in patients with rheumatic fever.[7, 8, 9] The periarteritis nodosa which was found at post mortem in the case we are reporting was diffuse and acute. For the following reasons we believe that it appeared after the onset of the bacterial endocarditis: (1) The onset of fever following a tooth extraction, leukocytosis, normal blood pressure, microhematuria and an apparently normal heart are all clinical findings consistent with the onset of right-sided bacterial endocarditis. (2) The elevation of the blood pressure during the second month of the illness, and increased leukocytosis and mild congestive heart failure, are features which suggest the clinical onset of periarteritis nodosa at that time. (3) Prior to admission the child had ap-

parently received neither sulfadiazine nor serum, substances which were shown by Rich and Gregory [10] often to cause periarteritis. (4) The microscopic pathology of marked fibrosis and lymphocytic infiltration beneath the endocarditis suggests that it was an older lesion than the acute necrotizing arteritis.

Summary

1. A case is presented of subacute bacterial endocarditis occurring on a patent foramen ovale in an otherwise normal heart. Only one similar lesion has been previously reported.

2. Histologically typical periarteritis nodosa was also found at post mortem. It appears to have developed some six to eight weeks after onset of the endocarditis.

BIBLIOGRAPHY

1. Barker, P. S.: A clinical study of subacute bacterial infection confined to the right side of the heart or the pulmonary artery, Am. Heart J. **37**: 1054, 1949.
2. Jacobius, H. L., and Moore, R. A.: Incidence of congenital cardiac anomalies in autopsies at New York Hospital, J. Tech. Methods **18**: 133, 1938.
3. Cosby, R. S., and Griffiths, G. C.: Interatrial septal defect, Am. Heart J. **38**: 80, 1949.
4. White, P. D.: Heart disease, 1944, The Macmillan Co., New York.
5. Roessler, H.: Interatrial septal defects, Arch. Int. Med. **54**: 339, 1934.
6. Bedford, D. E., Papp, C., and Parkinson, J.: Atrial septal defect, Brit. Heart J. **3**: 37, 1941.
7. Rothstein, J., and Welt, S.: Periarteritis nodosa in infancy and childhood, Am. J. Dis. Child. **45**: 1277, 1933.
8. Selye, H., and Pentz, E.: Pathogenetical correlations between periarteritis nodosa, renal hypertension and rheumatic lesions, Canad. M. A. J. **49**: 264, 1943.
9. MacIlwaine, Y.: The relationship between rheumatic carditis and subacute bacterial endocarditis, J. Path. and Bact. **59**: 557, 1947.
10. Rich, A. R., and Gregory, J. E.: The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity, Bull. Johns Hopkins Hosp. **72**: 65, 1943.

EDITORIAL

HOW TO PRESENT A SCIENTIFIC PAPER BEFORE A LARGE AUDIENCE

THE meetings of many medical societies now provide an audience that can number in the thousands, thanks to modern methods of voice amplification and visual projection. Such large audiences attract essayists whose work has won them high rank in their chosen field. Their names on programs, in turn, attract yet larger numbers. Unfortunately, a man who is top-flight as a scientist may nevertheless be most ineffectual on the lecture platform, usually because he makes some simple but crucial mistakes in his manner of presentation. Yet every such mistake is easily avoidable. On the basis of what this writer has suffered while listening to others at important meetings in the last thirty years, he is moved to offer some suggestions to future speakers.

If *you* have been invited to appear on some major program, it is hoped you will scan this editorial. You might find here a point or two that will help to make your presentation a bit more effective. If so, it will have been worth both the reading and the writing.

Time Limit: You have been assigned a fixed time limit for your entire appearance. Please note that this is an *outside limit,* that begins with the first word of introduction by the chairman and ends with the moment when you finish, or are requested to stand down. His words deduct about twenty seconds from the total time at your disposal, and you may lose even more if you are not as close as possible to the podium when called upon.

Of course, you have given your text several time trials in advance. All too often this results in your trying to read it a bit faster next time in order to get under the wire. What you really should do is shorten the text each time that it still seems too long. This can be done without sacrificing any vital point. Merely culling unnecessary words may be enough, and it teaches you to express clearly in a few words the thought that was obscured by verbosity.

Don't forget to include in your timing the demands of your lantern slides. Their text you have reckoned, of course. But you must also allow a few seconds for calling for the next slide, for looking at the slide to orient yourself, and for any "aside" that the moment may require. If the operator of the lantern gets a slide up-side down or out of order, the time lost in correcting this is nevertheless charged against your limit.

Remember that on the platform you must speak more slowly than in a classroom without the use of a loud speaker. Public-address systems in large auditoriums produce echos and reverberations: if you read deliberately, every word will be clearly heard; if you read rapidly, then your words will tend to run together and can become an unintelligible jargon. You should

therefore allow at least 15 per cent more time for platform reading than it takes in your timed trials reading slowly before the bathroom mirror.

Remember that the paper to be printed may be a page or two longer than the one you read, without offending either the editor or the reader. But no one can speak more than a limited number of words per minute without jamming the loud speaker and losing the listener. The worst sin against the time-limit, and the best way to ruin your prospects for future invitations by all who hear you, is to try to read a 23 minute paper in 20 minutes. But a 17-minute paper possesses the best ingredient for a successful presentation.

Microphone Technic: When you speak to an audience numbered in the thousands, you are 100 per cent dependent upon the correct use of the microphone 100 per cent of the time. If your technic is only 98 per cent correct, or if it is perfect only 98 per cent of the time, you will probably fail to get across far more than 2 per cent of your message, because the very words that failed to get through may have been the whole key to your thesis.

The microphone has strict limitations of performance which you must recognize. It magnifies by a *fixed* number that which you put into it. If it is *fixed* in space (for example, the microphone on the lectern), then you must maintain a *fixed distance* between your mouth and the microphone. This is best accomplished by holding with one hand to the edge of the lectern from start to finish. If you rock back and forth on your feet as you speak, or if you alternate between standing up straight and leaning confidentially on the lectern, you will alternately shout or whisper to your audience.

Your voice has its limitations, too. The chief ones are *direction, loudness* and *pitch*. The *direction* of your voice is straight *forward* and slightly *downward* from your mouth in a rather *narrow* beam. You should therefore speak only when facing the microphone, which should be at a level slightly *below* that of your mouth. The microphone will lose you, if you turn away and speak while looking at a lantern slide. Therefore, if you use slides, turn a moment in silence to see that the slide is right, then turn back to the microphone before you speak again. To a lesser extent, the microphone will lose you if your head bobs up and down as you look now at the audience, and now at your manuscript, especially if the microphone is at a *higher* level than your mouth.

Loudness of your voice is in part a factor of the effort you put into it. But loudness is also related to *pitch:* the lower the pitch, the less loud the sound you produce. When you speak in a conversational tone in a small group, the ends of your sentences are audible only to those nearest you. If you are a good speaker in a class room without the aid of an amplifier, it is because you have learned to keep both loudness and pitch up, so that the man in the back row can hear each word.

The microphone is rather like a person with catarrhal deafness: it hears you well only while you keep the pitch of your voice up, and the loudness

adequate. But it fails to hear you if pitch or loudness falls too low. What is equally important, if you speak too loudly, your voice blares and becomes painfully unintelligible.

Loudness, as picked up by the microphone, varies to an extreme degree with the distance between mouth and microphone. If that distance is only one or two inches, then the voice should be soft, low-pitched and confidential, and the same distance must be scrupulously maintained to avoid wide output fluctuations. This is a method that expert announcers use to good advantage. On a speaker's platform it is useful only if there is a portable microphone that can be held evenly and constantly before the mouth as the speaker points to slides, looks at people on the platform or moves about. It is not a good method when there is a fixed microphone and you are reading from a text.

If the distance between mouth and microphone is too great, then the man at the controls of the amplifier is forced to turn up full power in the attempt to catch your voice. If you are not too far away, he may succeed; but often he only produces a loud ringing screech that stops the entire proceedings.

The *best distance* between mouth and a fixed lectern microphone is 7 to 10 inches: at this distance, minor movements of the head produce less fluctuation in loud-speaker output than do the same movements when you are only an inch or so away. The distance is easy to measure by the span of the hand: thumb your chin (not your nose) to the microphone.

The most desirable *loudness* at this distance is that which you would use in speaking to a group of fifty in a classroom, being careful not to drop the pitch too low at the ends of sentences.

Nothing must come between your mouth and the microphone. Every time you scratch your nose or rub your lip, your hand sharply reduces the volume of sound delivered. It is even worse to hold your manuscript in such a way as to blanket the microphone.

Lantern Slides: Visual aid by lantern slides is extremely useful to illustrate something by picture, to convey a concept by diagram, and to emphasize salient facts or data, provided your slide technic is good. But a poor *slide technic* can ruin your presentation even more surely than can any of the mistakes thus far mentioned. Here are the chief points to be kept in mind to get the best results:

The *number* of slides to be shown is a function of the time limit assigned. It usually takes over one minute per slide: very few take less and some considerably more. Repeated time trials for the slides are more important to make than those for text, since slides are more likely to go overtime and harder to speed up.

The *size* of slides should correspond, whenever possible, to that of the standard projector available: 3¼ by 4 inches. If for any reason some other size must be used, be sure not only to get confirmation in writing, and well

in advance, of the availability of the size and type of projector you require, but to verify its presence before the meeting starts.

Have your material *centered* and well within the projectable portion of the slide. This will save you the embarrassment of having a picture decapitated, or the total at the foot of a column chopped off, or the beginnings or ends of lines of text deleted, and also the unanticipated loss of time in asking the operator to shift the slide or raise or lower the lantern.

Top and bottom are cut off more frequently, especially if you arrange your material in a rectangle whose long dimension is perpendicular. Such slides work perfectly in all classrooms, where the screen is *square*. But in nearly every large auditorium, the screen is *rectangular*, with the long dimension *horizontal*, because the screen is intended primarily and solely for the projection of motion picture film, whose frames are rectangles that are invariably horizontal.

But the lateral edges are also vulnerable, because in a large auditorium the projection lantern is placed as far back as possible in order to get the maximum of magnification which the full width of the screen will allow. Therefore, use a *mat*, to be sure your material is properly centered and limited: the opening of the mat should not exceed 2½ by 3 inches.

If the slide presents a *picture* or a *photomicrograph*, make use of such devices as an arrow, or circle, to call prompt attention to the important features. As you talk about the slide, you can then mention the ringed area, without using the pointer that someone forgot to provide. Be sure to write out every word of your comment on the slide, so that it, too, will be properly timed.

The use of the *electric torch: arrow pointer* calls for comment. Get to the meeting place early to familiarize yourself with this useful gadget. In using it, point it at once to the item you mean to stress, and turn it off promptly when that purpose has been served, or else point it directly at your feet until you need it again. It is most disconcerting for the audience to follow the arrow's aimless wanderings all over the screen in anticipation of another point of emphasis that never comes. Between applications, don't shine it in the faces of those in the front row, or that of the chairman.

If the slide presents a *diagram* or *figure*, this should be so *simple* that it can be grasped within seconds and understood without reference to a blue print. The use of *contrasting colors* makes the figure more intelligible and easier to explain.

If the slide presents *data*, these should be minimal in number. Those which are most significant should be so designated by means of contrasting colors, or bold-faced type, or underlining, or combinations of these devices.

If the slide presents *facts* in text form, they should be few, arranged preferably in outline form, and with the separate members of the outline identified by numbers.

In planning the *arrangement* of all slide material, take a leaf out of the

book of the commercial advertiser. He knows he has only seconds to catch the eye of the public: so he uses the simplest picture, the fewest words, the brightest colors, the biggest type for the most important thought, all to make the most striking effect at a glance.

Visibility by the man in the last row is the chief factor that limits the amount of material that should go on a slide. In order to be just legible, the width of every part of a letter must subtend an angle of 1′, and the height and width of the whole letter must subtend an angle of 5′; that is, an angle whose apex is at the pupil of the viewer and which has an opening of 5′, the overall dimension of the letter. This fact is the basis of the Snellen Test Chart for measuring visual acuity. Now to subtend an angle of 5′ at the pupil of the man in the last row 200 feet from the screen, the letter on the screen must be 3 inches high and wide. (Multiply the distance from the screen by 0.001425 to get the dimension of the letter.) If the screen is 15 feet wide, then a single line of text on the screen can have no more than 60 letters and spaces, if that text is to be *just readable* by a man in the last row, if he has 20/20 vision. To be *easily readable*, the line must have decidedly fewer letters and spaces. To be safe in planning your slides, you must know the size of the screen and its distance from the back row.

Leave the slide on the screen long enough for everyone to read it. This usually takes half-again as long for the other fellow as it does for you, so give him a break in your timing.

It is better *to signal for the next slide with a buzzer* or "clicker," if available, than to say "next slide," lest the operator mistake a word in your text for such a signal. A recent speaker lost valuable time because the operator shifted slides when he heard the word, "Dextran."

These have been the *"Do's"* to be observed in lantern slide technic. Even more important are the *"Don't's."*

The most important one is this: *Don't put too much on a slide.* If it is a picture or a photomicrograph, don't have too much irrelevant material, such as the whole cross-section of an organ, thereby dwarfing into insignificance the crucial part of the picture. If you wish to show proportion or relations, then use a second slide for further detail.

Don't project a complicated diagram: it takes too long to decipher.

Don't put too many data on a single slide, especially irrelevant data. Yet this unhappy mistake is the one most frequently committed: the author is too lazy to construct a brief summary of salient data, so he photographs instead a detailed table that will occupy a full page in the printed paper.

Don't project whole paragraphs of running text. Use outline form and telegraphic style to get the few important facts across most quickly. If there are more facts, use two slides.

Don't distract your audience in any of the following ways: Don't talk away from the slide on the screen: your comments should be to emphasize or amplify what is in sight, not to present new ideas. Don't leave a slide

on the screen when it is no longer needed. If you have something new to say before going on to the next slide, ask for "lights, please," or signal the operator by means of a blank slide or by a white card properly placed in your series of slides.

Don't frustrate your audience by whisking a slide off the screen before they have had time to read it.

Don't waste the time of your audience by reading every word and figure on the screen. They can read, too, so confine yourself to brief relevant comments.

Don't use slides with white letters on a black background: their visibility is much less than that of slides with black letters on a white background.

These, then, are the general principles that underlie the proper and effective presentation of a scientific paper before a large audience, and to these the writer has decided to confine himself. But please do not think that your personal problems in presentation have been fully covered in the foregoing advice. They require special study and individual analysis.

Fortunately, you don't have to depend upon your best friend or severest critic to do this for you, although they can be most helpful. It is today a simple and inexpensive matter to have a tape recording made of one of your efforts at public speaking. Then, at first alone, and later in the company of an honest critic, play it back to yourself many times, making notes and encouraging the critic to interrupt.

When you have recovered from the first shock of hearing the voice of an utter stranger come back to you out of the machine, you can begin objectively to assess your most obvious mistakes of presentation: the hurried delivery, the monotonous intonation, the failure to pause between paragraphs, or before important points, as you race through your text. Then, at times when you leave your script and "ad lib" a bit, note the slowness, also the hesitation as you grope for the next word; the falling pitch that kills the ends of sentences, especially if the last word is a proper noun; and all the irrelevant "ah's" and "uh's" that eat up so much precious time; and the disconcerting noises, when every few sentences you nervously clear your throat.

Now, if your ego can still take it, have a motion-picture as well as a sound-track recording made of one of your presentations. See for yourself your distracting, and therefore undesirable habit of scratching your face, rubbing your nose, twisting your ear or tugging on a lock of hair. Do you ever look at the people you are trying to impress, or are your eyes glued to your manuscript? And what of your gestures? Gestures, like spices, add zest and interest, if unobtrusive, appropriate to the matter in hand, and if used sparingly; but better no gestures than too many or the wrong ones, awkwardly made. Their proper use calls for native talent as well as careful training.

This article has been written about the proper presentation of a scientific paper, an infrequent and ephemeral activity, indeed, as far as most of us are

concerned. Yet it is an aspect and an actual part of a much more important function in the lives of most of us who present papers: the function of teaching. If you are a teacher, then regardless of your specialty in medical science or practice, you should realize that medical pedagogy is as much a specialty as is chemistry or pediatrics. If you are a teacher, it is your responsibility to perfect yourself in pedagogy as well as in your branch of knowledge, in order to bring your teaching mission to its highest fruition: not only to know, but to be able to impart to others what you know. If you are or hope to be a teacher, this editorial deserves a second reading.

RICHARD A. KERN, M.D., F.A.C.P.,
Secretary General, American College of Physicians

REVIEWS

Heart Disease. 4th Ed. By PAUL D. WHITE, M.D. 1015 pages; 16 × 24 cm. The Macmillan Company, New York. 1951. Price, $12.00.

This text and its author are deservedly famous and need little introduction to English-speaking cardiologists and internists.

The sober and unadorned exterior of the last wartime edition has given place to a more modern appearance which prompts the doubting mind to wonder if the kernel has kept pace with its shell. Doubts, however, are soon dispelled by the traditional excellence of the current edition.

A new introductory historical chapter, The Evolution of Our Knowledge of the Heart and Its Diseases, is well worth reading. The body of the text remains divided into four parts. Part I, on Methods of Cardiovascular Examination and on Symptoms and Signs, has been augmented by suitably brief and cautious accounts of the new technics of electrofluorokymography and ballistocardiography. The chapter on electrocardiography has been partly rewritten and now includes a short section contributed by Dr. J. W. Hurst on vectorcardiography. This contribution is inadequate either to clarify the subject to the uninitiated or to convert sceptics to the new doctrine.

Part II continues to present the Prevalence, Causes and Types of Heart Disease —in Dr. White's opinion the most important part of his book. Parts III and IV, as before, deal respectively with Structural Cardiovascular Abnormalities and Disorders of Cardiovascular Function. These sections are little changed with only minor rearrangements and additions to bring the work up to date.

Dr. White has an enviable lucidity of style, blemished only by the frequent use of unnecessarily long sentences. Yet he has the happy faculty of being able to carry the reader with him through a maze of clauses from which the reader usually emerges with the meaning clear. At times, however, the author outdoes himself and loses the bewildered reader on the way.

One important inaccuracy has been perpetuated from previous editions. In the section dealing with pulsus paradoxus (page 161), Dr. White still contrasts this abnormality of the pulse with "the usual increase of the pulse fullness during inspiration and its decrease during expiration in the case of normal diaphragmatic breathing." But it is surely common knowledge that the normal pulse tension tends to decrease with inspiration and increase with expiration. Pulsus paradoxus is a pathological *exaggeration* of this normal fluctuation.

The book retains its very desirable complement of historical quotations and word derivations. Indeed it bears throughout the stamp of both the scholar's and the master physician's touch, and it continues to be one of the best all round textbooks available on any medical subject.

H. J. L. M.

Clinical Ballistocardiography. By HERBERT R. BROWN, JR., M.D., VINCENT DELALLA, JR., M.D., MARVIN A. EPSTEIN, M.D., and MARVIN J. HOFFMAN, M.D., Department of Medicine, University of Rochester, School of Medicine and Dentistry. 188 pages; 14.5 × 22 cm. 1952. The Macmillan Company, New York. Price, $5.50.

This small volume is the first to appear on the subject of ballistocardiography. The sections on the history of the ballistocardiogram, on the types of apparatus, and the physical considerations in the construction of a ballistocardiograph are very in-

teresting. The normal ballistocardiogram is described, but no statement is made as to how often "normal" ballistocardiograms are encountered in patients with clinical heart disease, and how often "abnormal" ballistocardiograms are found in patients with no clinical evidence of cardiovascular disease. As the authors state, "The full limits of a 'normal pattern' have yet to be defined, and the significance of certain deviations from the 'normal' . . . are not fully understood." The discussion creates the impression that there are a number of specific ballistocardiographic patterns for various diseases, and that the ballistocardiogram yields information of value as a diagnostic tool and as a prognostic aid. Actually, the state of knowledge concerning the mechanism and meaning of the various deflections of the ballistocardiogram is incomplete and in its infancy, and its clinical usefulness is yet to be determined. This volume therefore seems to be premature in appearance. The historical and technical chapters are of especial value but the clinical sections should be read with some reserve.

S. S.

A Symposium on Essential Hypertension: An Epidemiologic Approach to the Elucidation of Its Natural History in Man. A State Document of The Commonwealth of Massachusetts, published under special legislative act. 373 pages; 15.5 × 23.5 cm. Wright and Potter Printing Company, Legislative Printers; distributed by the Secretary of the Commonwealth, Room 116, State House, Boston 33. 1951. Price, $3.95.

As is stated in the sub-title of this book, this symposium represents an epidemiologic approach to the elucidation of the natural history of essential hypertension in man. It is the result of a study by a recess commission of the Massachusetts General Court which is to determine what, if any, action the Commonwealth should take in the control and treatment of high blood pressure. The symposium comprises a series of five sections: Section I defines terms, establishes criteria and introduces a concept of the natural history of essential hypertension. Section II considers the elucidation of causes of essential hypertension. Sections III and IV review the parts played by specific agents, the environment and human characteristics in the initiation and perpetuation of the disorder. Section V appraises current knowledge and introduces a proposal for community research.

Contributing to the symposium are epidemiologists, sociologists, clinical and laboratory investigators, psychiatrists, practicing physicians, and surgeons. The participants are individuals well known in the field of hypertension and their presentations are of a uniformly high calibre. Following each section of the symposium is an extremely well edited discussion which appears to be unusually complete and of as much value as the formal presentations.

This symposium can be recommended wholeheartedly to any one interested in the problems of essential hypertension.

L. S.

The Thoracic Surgical Patient—Preoperative, Anesthetic and Postoperative Care. By Lew A. Hochberg, M.D., Foreword by Frank B. Berry, M.D. 364 pages; 15.5 × 23.5 cm. Grune & Stratton, Inc., New York. 1952. Price, $8.75.

This book is an attempt on the part of the author and other contributors to recapitulate those things which they have found to be helpful in the care of the thoracic surgical patient. In it is emphasized the complete care of the thoracic surgical patient from the varied points of view of the intern, resident surgeon, physician, surgeon, anesthesiologist, and physiatrist. Included are discussions of physiology and pathologic physiology, endoscopy, anesthesia, chest injuries, empyema, collapse therapy, pul-

monary resection, surgery of the esophagus, diseases of the mediastinum, diaphragmatic hernia, cardiovascular surgery, and rehabilitation.

Particularly good are the chapters on anesthesia and rehabilitation. Many readers will be disappointed by the comparatively small space devoted to cardiovascular surgery.

The specific recommendations on cardiac arrhythmias, failure, quinidine, digitalis and pronestyl are subject to much question and in several instances appear to the reviewer dangerous if applied as indicated. The discussions appear inadequate on cardiac physiology, injuries to the heart, angiography, the differential diagnosis of thoracic tumors, and in several other important subjects.

It is interesting to note that there is no internist present in the list of contributors. Such an individual may very well be necessary not only in the preoperative and postoperative care of a thoracic surgical patient, but also in correcting many of the inadequacies of this book.

L. S.

The Diagnosis and Treatment of Intrathoracic New Growths. By MAURICE DAVIDSON, M.A., D.M., B.Ch. Oxon., F.R.C.P. London, Consulting Physician to the Brompton Hospital for Consumption and Diseases of the Chest; Consulting Physician to the Miller General Hospital for South-East London; Consulting Physician to the Western Ophthalmic Hospital; Sometime Associate Physician to the Royal Cancer Hospital. With a chapter on Radiotherapy by DAVID W. SMITHERS, M.D. Cantab., M.R.C.P. London, D.M.R., Professor of Radiotherapy, University of London; Director of the Radiotherapy Department, Royal Cancer Hospital. Also a chapter on Operative Treatment by OSWALD S. TUBBS, M.A., M.B., B.Chir. Cantab., F.R.C.S. Eng., Thoracic Surgeon to St. Bartholomew's Hospital; Assistant Surgeon to the Brompton Hospital. 260 pages; 17.5 × 25 cm. Oxford University Press, New York. 1952. Price, $8.75.

This text is a complete survey of intrathoracic new growths. It is not a surgical text but is addressed to all physicians who are directly or indirectly concerned with lung cancer and other growths in the chest. Classification of tumors in this volume is not made on an anatomical basis, but according to pathological structure. The authors have presented a full picture of the subject and include a discussion of the apparent increase in lung cancer. They stress also the importance of early diagnosis and treatment.

Each type of tumor is presented separately and in an orderly fashion, including differential diagnosis, pathology and treatment. Ample illustrations are used throughout. Treatment, both radiological and surgical, is carefully discussed in separate sections.

This volume presents the present position of medicine, surgery and radiology in the diagnosis of intrathoracic new growths and should become a welcome contribution to the field.

R. A. C.

The Child in Health and Disease. By CLIFFORD G. GRULEE, M.D., and R. CANNON ELEY, M.D. 1255 pages; 18 × 26 cm. The Williams and Wilkins Co., Baltimore. 1952. Price, $15.00.

The second edition has been brought up to date by extensive revisions and additions. It has been enlarged approximately 200 pages so that it contains 1,208 pages of rather small print in double columns. New chapters have been added concerning adoptions, management of summer camps, erythroblastosis fetalis and cystic fibrosis of the pancreas. While varying from author to author, the style tends to be rather

informal. This informality lends personality and interest at times, but also tends to decrease the conciseness and completeness of some of the presentations. There are numerous errors of composition and typography. The daily dosage of 10 "milligrams" of B_{12} on page 105 should apparently be micrograms.

Since much of the subject matter of such a progressive field of clinical medicine is a matter of opinion with different authorities on the same subjects having different conceptions and points of emphasis, the existence of various books presenting the view points of different authors seems highly desirable. The present volume thus serves a valuable function as a reference book in pediatrics.

G. E. G.

BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Adrenal Cortex: Transactions of the Third Conference, November 15–16, 1951, New York, N. Y. Edited by ELAINE P. RALLI, Department of Medicine, College of Medicine, New York University. 204 pages; 23.5×15.5 cm. 1952. Sponsored by the Josiah Macy, Jr. Foundation. Price, $3.25.

The Autonomic Nervous System: Anatomy, Physiology, and Surgical Application. 3rd Ed. By JAMES C. WHITE, M.D., Associate Professor of Surgery, Harvard Medical School, etc.; REGINALD H. SMITHWICK, M.D., Professor and Chairman of the Department of Surgery, Boston University School of Medicine, etc.; and FIORINDO A. SIMEONE, M.D., Formerly Assistant Professor of Surgery, Harvard Medical School, etc. 569 pages; 24.5 × 16 cm. 1952. The Macmillan Company, New York. Price, $12.00.

Basic Principles of Cancer Practice: A Book on Diagnosis, Prognosis, and Treatment of Human Neoplasms for the General Practitioner and Medical Student. By ANDERSON NETTLESHIP, M.D., F.A.C.P., Fellow, New York Academy of Medicine, etc. 398 pages; 23.5 × 15.5 cm. 1952. The Williams & Wilkins Co., Baltimore. Price, $7.00.

The Clinical Application of Antibiotics: Penicillin. (This volume, although a separate publication, is a continuation of the work described in *Antibiotics* Volumes I and II, and may be read in conjunction with it.) By M. E. FLOREY, M.D., from the Sir William Dunn School of Pathology, Oxford. 730 pages; 25.5 × 16 cm. 1952. Oxford University Press, New York. Price, $17.50.

Correlative Cardiology: An Integration of Cardiac Function and the Management of Cardiac Disease. By CARL F. SHAFFER, M.D., F.A.C.P., Associate Professor of Clinical Medicine, Baylor University College of Medicine, and DON W. CHAPMAN, M.D., F.A.C.P., Associate Professor of Medicine, Baylor University College of Medicine. 525 pages; 24 × 16 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $9.50.

Culdoscopy: A New Technic in Gynecologic and Obstetric Diagnosis. By ALBERT DECKER, M.D., D.O.G., F.A.C.S., Clinical Professor of Gynecology and Obstetrics, New York Polyclinic Medical School and Hospital, etc.; with a Foreword by RICHARD W. TELINDE, M.D. 148 pages; 21.5 × 14 cm. (paper-bound). 1952. W. B. Saunders Company, Philadelphia. Price, $3.50.

Expert Committee on Health Statistics: Third Report, including Second Report of the Subcommittee on the Registration of Cases of Cancer as Well as Their Statistical Presentation. World Health Organization Technical Report Series No. 53. 54 pages; 24 × 16 cm. (paper-bound). 1952. World Health Organization, Geneva; Agents in U.S.A.: Columbia University Press, International Documents Service, New York. Price, 35 cents.

Manual of Electrocardiography. By BENJAMIN F. SMITH, M.D., Professor of Clinical Medicine, Baylor University College of Medicine, etc. 215 pages; 23.5 × 15.5 cm. 1952. Elsevier Press, Inc., Houston. Price, $4.50.

Medical Aspects of Civil Defense: Series of Special Articles Reprinted from The Journal of the American Medical Association, A Copyrighted Publication. Council on National Emergency Medical Service, JAMES C. SARGENT, M.D., Chairman, Milwaukee, Wisconsin. 21.5 × 14 cm. (paper-bound); 130 pages. 1952. Reproduced by Council on National Emergency Medical Service, Chicago. Price, 25¢ per copy; 20¢ per copy for orders of 100 or more.

Ophthalmic Glossary. By M. R. GOLDMAN, M.D., Assistant in Department of Ophthalmology, Montefiore and Passavant Hospitals, Pittsburgh, Pennsylvania. 40 pages; 28 × 22 cm. (paper-bound, loose-leaf). 1952. Richard Rimbach Associates, Pittsburgh. Price, $2.50.

Die Osteomalazie. By DR. MED. MARKUS WERNLY, Bern. 101 pages; 24 × 17 cm. (paper-bound). 1952. Georg Thieme Verlag, Stuttgart; Agents for U.S.A.: Grune & Stratton, New York. Price, Kart. DM 14.40.

The Principles and Methods of Physical Diagnosis: Correlation of Physical Signs with Physiologic and Pathologic Changes in Disease. By SIMON S. LEOPOLD, M.D., Associate Professor of Clinical Medicine, School of Medicine and Graduate School of Medicine, University of Pennsylvania, etc.; with a Chapter on "Sounds from the Thorax: Acoustic Principles" by S. REID WARREN, JR., Sc.D. in E.E., Professor of Electrical Engineering, the Moore School of Electrical Engineering, University of Pennsylvania. 430 pages; 24 × 16 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $7.50.

Recent Advances in Medicine: Clinical, Laboratory, Therapeutic. 13th Ed. By G. E. BEAUMONT, M.A., D.M. (Oxon.), F.R.C.P., D.P.H. (Lond.), Physician to the Middlesex Hospital, etc.; and E. C. DODDS, M.V.O., D.Sc., Ph.D., M.D., F.R.C.P., F.R.I.C., F.R.S. (Edin.), F.R.S., Courtauld Professor of Biochemistry in the University of London, etc. 397 pages; 21 × 13.5 cm. 1952. The Blakiston Company, Philadelphia. Price, $6.00.

Renal Function: Transactions of the Third Conference, October 18–19, 1951, New York, N. Y. Edited by STANLEY E. BRADLEY, Department of Medicine, College of Physicians and Surgeons, Columbia University. 210 pages; 23.5 × 15.5 cm. 1952. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $3.50.

St. Thomas's Reports. Second Series. Volume VII. Editorial Committee: DR. J. H. CYRIAX, DR. H. K. GOADBY, MR. R. W. NEVIN, DR. J. S. RICHARDSON, MR. B. K. RICKFORD and DR. H. J. WALLACE. 184 pages; 25.5 × 16 cm. 1951. St. Thomas's Hospital, London. Price, 10s. 6d.

Transactions of the 11th Conference on the Chemotherapy of Tuberculosis, Held on January 17 to 20, 1952, at the St. Louis Medical Society, St. Louis, Missouri. Prepared and Edited by Veterans Administration Area Office St. Louis, Mo. and Central Office Washington 25, D. C. 401 pages; 26 × 20 cm. (paper-bound). 1952. Price: Not for sale to individuals; Free to Libraries.

The Treatment of Diabetes Mellitus. 9th Ed. By ELLIOTT P. JOSLIN, A.M., M.D., Sc.D., Medical Director, George F. Baker Clinic, New England Deaconess Hospital, etc.; HOWARD F. ROOT, M.D., Physician, New England Deaconess Hospital, etc.; PRISCILLA WHITE, M.D., Sc.D., Physician, New England Deaconess Hospital, etc.; and ALEXANDER MARBLE, A.M., M.D., Physician, New England Deaconess Hospital, etc. 771 pages; 24 ×15.5 cm. 1952. Lea & Febiger, Philadelphia. Price, $12.00.

The Treatment of Injuries to the Nervous System. By DONALD MUNRO, M.D., F.A.C.S., Surgeon-in-Chief, Department of Neurosurgery, The Boston City Hospital, etc. 284 pages; 24 × 16 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $7.50.

Veterans Administration Technical Bulletins, Series 10. Volume V, 1951. 166 pages; 27 × 20.5 cm. 1952. Veterans Administration, Washington. Price: Not for sale—limited edition for distribution to VA hospitals and medical libraries.

Die Vitamine und ihre klinische Anwendung. By DR. MED. W. STEPP, DR. MED. J. KÜHNAU and DR. PHIL. DR. MED. H. SCHROEDER. 535 pages; 25 ×16 cm. 1952. Ferdinand Enke Verlag, Stuttgart. Price, Geheftet DM 52.—; Ganzleinen DM 56.—.

COLLEGE NEWS NOTES

New Life Members

The College takes pleasure in announcing that the following Fellows have become Life Members of the American College of Physicians since the publication of the last issue of this journal:

Dr. Albert Hanley Held, Beverly Hills, Calif.
Dr. Julius Kahn, Beverly Hills, Calif.
Dr. J. Harry Murphy, Omaha, Nebr.
Dr. James A. Barr, Oakland, Calif.
Dr. Michael A. Ogden, Passaic, N. J.
Dr. Thomas G. Hobbs, Lexington, Ky.
Dr. Frieda Baumann, Philadelphia, Pa.

A.C.P. Regional Meetings

West Virginia initiated its first A.C.P. Regional Meeting at White Sulphur Springs, July 25, 1952, under the Governorship of Dr. Paul H. Reverecomb and through the coöperation of the West Virginia State Medical Association. The State society assigned an appropriate time during its Annual Meeting, and the program was made up for the American College of Physicians and members of the State society invited to attend as well as members of the College. A reception and banquet of the College members were held in the evening. Dr. T. Grier Miller, Philadelphia, President of the College, was the guest speaker at the banquet; he also addressed one of the scientific sessions of the State society. A large proportion of the College members from West Virginia were present; the program was superior; the meeting, exceptionally successful.

North Dakota held its annual Regional Meeting at Grand Forks, September 13, 1952, with a program made up almost exclusively by Associates of the College, giving these young men the opportunity and stimulation of presenting important work they have been pursuing. Dr. C. H. A. Walton, F.A.C.P., A.C.P. Governor for Manitoba and Saskatchewan, was the guest speaker at the banquet. Although the College membership in North Dakota is limited in numbers, practically every member was in attendance, and many non-member physicians attended as guests. The North Dakota Regional Meeting is always effective and stimulating. Dr. R. B. Radl, Bismarck, is the Governor.

The following Regional Meetings are already scheduled and others are in course of organization:

1952

Western New York—Syracuse, October 3
Dr. E. C. Reifenstein, Sr., Syracuse, Governor;
Dr. T. Grier Miller, Philadelphia, President,
Dr. C. F. Moffatt, Montreal, 2nd Vice President,
Dr. E. L. Amidon, Burlington, Governor for Vermont,
Dr. Karver L. Puestow, Madison, Governor for Wisconsin,
Dr. W. R. Willard, Dean, State University of New York College of Medicine at Syracuse, and
Mr. E. R. Loveland, Philadelphia, Executive Secretary, Special Guests

Montana-Wyoming—Great Falls, Mont., October 10–11
Dr. Harold W. Gregg, Butte, Mont., Governor
Dr. Walter L. Palmer, Chicago, (Regent) Special Guest
Pacific Northwest—Vancouver, B. C., October 17–18
Dr. John W. Scott, Edmonton, Governor and Chairman
Dr. George Davidson, Vancouver, Program Chairman
Dr. T. Grier Miller, Philadelphia, (President) Special Guest
Oklahoma—Oklahoma City, October 27
Dr. Wann Langston, Oklahoma City, Governor
Dr. George F. Lull, Chicago, Special Guest
Arizona-New Mexico—Albuquerque, October 29
Dr. Walter I. Werner, Albuquerque, Governor and Chairman
Dr. Dwight L. Wilbur, San Francisco, (Regent) Special Guest
New Jersey—Newark, November 5
Dr. Edward C. Klein, Jr., South Orange, Governor
Dr. Henry Crossfield, East Orange, Program Chairman
Dr. T. Grier Miller, Philadelphia, (President), Special Guest
Southeastern—Havana, Cuba, November 7, 8 and 9
Dr. Jose Centurion, Havana, Local Governor
Dr. Angel Vieta, Havana, Program Chairman
Drs. Robert Wilson, Jr., Carter Smith, William C. Blake and D. O. Wright, Participating Governors;
Dr. T. Grier Miller, Philadelphia, President,
Dr. Edward L. Bortz, Philadelphia, Regent, and
Mr. E. R. Loveland, Philadelphia, Executive Secretary, Special Guests
Midwest—Chicago, November 22
Dr. Howard Wakefield, Chicago, Local Governor and General Chairman
Dr. T. Grier Miller, Philadelphia, (President), Special Guest
Kentucky—Lexington, November 29
Dr. J. Murray Kinsman, Louisville, Governor
Dr. John Harvey, Lexington, Chairman
Dr. Richard A. Kern, Philadelphia, (Secretary-General), Special Guest
North Carolina—Winston-Salem, December 4
Dr. Elbert L. Persons, Durham, Governor
Dr. T. Grier Miller, Philadelphia, (President), Special Guest

1953

Eastern Pennsylvania—Philadelphia, January 16
Dr. Thomas McMillan, Philadelphia, Governor
Colorado—Denver, February 17
Dr. C. F. Kemper, Denver, Governor
Dr. Frank T. Joyce, Denver, Chairman
Dr. Howard P. Lewis, Portland, (Regent), Special Guest
Virginia—City to be announced, February 26
Dr. Charles M. Caravati, Richmond, Governor
Delaware—Wilmington, February 27
Dr. Lemuel C. McGee, Wilmington, Governor;
Dr. T. Grier Miller, Philadelphia, President,
Dr. Richard A. Kern, Philadelphia, Secretary-General, and
Mr. E. R. Loveland, Philadelphia, Executive Secretary, Special Guests
Kansas—Kansas City, March 20
Dr. William C. Menninger, Topeka, Governor
Dr. Lee H. Leger, Kansas City, Chairman
Dr. T. Grier Miller, Philadelphia, (President), Special Guest

Programs of the Regional Meetings customarily are mailed only to the members in the states or provinces directly participating. Others who are interested may obtain programs on request to the Executive Secretary of the College, 4200 Pine St., Philadelphia 4, Pa.

Tele-Clinic Film of Cleveland Annual Session Now Available

A Tele-Clinic film depicting the highlights and events of the 33rd Annual Session of the American College of Physicians, held at Cleveland, Ohio, April 21–25, 1952, has now been completed, and is ready for showing before Regional Meetings of the College or at special meetings of physicians, at medical societies, hospital staff meetings, etc. The film is underwritten through the courtesy of Wyeth, Inc., of Philadelphia. They have presented one film to the College Library, and have numerous copies of the film available so that the film may be shown at more than one place at one time.

Oklahoma Will Hold Special A.C.P. Dinner

Dr. Wann Langston, F.A.C.P., Governor for Oklahoma, has announced a get-together dinner of the members of the College from Oklahoma on the evening of October 27, during the Oklahoma City Clinical Society Meeting. Dr. George F. Lull, F.A.C.P., General Secretary of the American Medical Association, will be the special guest.

During the early part of 1952, Oklahoma and Arkansas joined with the Midsouth Regional Meeting at New Orleans, and will hold no special Regional Meeting with a scientific program during 1952. This general dinner meeting is arranged to preserve interest of the members in that area. In 1953, Oklahoma and Arkansas will combine in holding a Regional Meeting, probably in Oklahoma City.

Supplement to 1951 Directory of the American College of Physicians

A Supplement to the 1951 Directory of the American College of Physicians containing the names and biographical data of members elected November, 1951, and April, 1952, has been compiled. Copies will be mailed free of charge to all subscribers to the 1951 Directory. The next complete Directory of the College will be published in 1953.

Correction, July, 1952, News Item

In the July issue of this journal in the News Notes Section, it was announced that Dr. Harold J. Jeghers, F.A.C.P., Professor of Medicine at Georgetown University School of Medicine, has been appointed director of a new venture in postgraduate medicine. St. Mary's Hospital, erroneously listed as Rochester, Minnesota, should have been designated as Rochester, New York. That Hospital has become affiliated with Georgetown University School of Medicine in order to augment teaching facilities. Under the program, full-time staff members of the School of Medicine of Georgetown University will visit St. Mary's Hospital monthly for periods of four or five days; residents and interns will be rotated for brief periods through the Georgetown Center, and St. Mary's attending staff members will also visit for special instruction and observation.

Coming Examinations by Certifying Boards

The American Board of Internal Medicine, William A. Werrell, M.D., Secretary-Treasurer, 1 West Main St., Madison 3, Wis.

1953 Oral Examinations:
New Orleans, La.—February 3–6; Philadelphia, Pa.—Week preceding A.C.P. Thirty-Fourth Annual Session; New York City—Week preceding A. M. A. annual meeting.

The American Board of Pediatrics, John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Road, Rosemont, Pa.

Oral Examinations:
Chicago, Ill.—October 24–26, 1952; Boston, Mass.—December 5–7, 1952.

Hahnemann Medical College Establishes a Student Research Fund

Dr. Charles L. Brown, F.A.C.P., Dean of Hahnemann Medical College and Hospital of Philadelphia, has established a Student Research Fund, the nucleus being a balance of some $1760.00, net income from a postgraduate course in Internal Medicine directed by him for the American College of Physicians during the past spring.

Each summer there are two or three outstanding students at the Hahnemann Medical College who are willing and able to remain there for two months to work on research problems in the pre-clinical years as assistants to some member of the faculty in those departments. The Student Research Fund will be used to assist these students with living and other expenses, and it is hoped this will be a highly appropriate manner of utilizing the surplus from the A.C.P. course.

American Heart Association Seeks New Research Applicants

New research applications in the cardiovascular and related fields are now being accepted by the American Heart Association for studies to be conducted during the year beginning July 1953, it has been announced by Dr. Louis N. Katz, F.A.C.P., Chairman of the Association's Scientific Council.

Applications for Research Fellowships and Established Investigatorships should be submitted by September 15, 1952. Applications for Research Grants-in-Aid may be filed up to December 1, 1952. Information and forms may be obtained from the Medical Director, American Heart Association, 1775 Broadway, New York 19, N. Y. Applications will be reviewed by the Research Committee of the Scientific Council.

Awards will be made from funds raised in the 1952 Heart Fund campaign by the American Heart Association and its affiliates throughout the nation.

Research Fellowships are open to graduates of approved medical and graduate schools who are interested in research and who plan to follow an academic career. Established Investigatorships are open to individuals of proved ability who have the degree of Doctor of Medicine, Doctor of Philosophy, Doctor of Science, or the equivalent, and who are interested in a career in research. Grants-in-aid are available to non-profit institutions for a specified program of research including work in the basic sciences, under the direction of an experienced investigator.

The Research Fellowships, which are granted for a one-year period, range from $3,500 to $5,500. Established Investigatorships, which may be extended annually for a five-year period, range from $6,000 to $9,000. Grants-in-aid are awarded in varying amounts, usually not exceeding $10,000, and the period covered is variable, depending on the particular program of study.

American Goiter Association Announces Van Meter Prize Award

The American Goiter Association again offers the Van Meter Prize Award of $300.00 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the Annual Meeting of the Association, Chicago, Ill., May 7, 8 and 9, 1953, provided essays of sufficient merit are presented in competition.

A place will be reserved on the program of the Annual Meeting for the presentation of the Prize Award Essay by the author, if it is possible for him to attend. For full details write to the Corresponding Secretary, Dr. George C. Shivers, 100 East Saint Vrain Street, Colorado Springs, Colo., not later than February 15, 1953.

Twenty-Fifth Graduate Fortnight of the New York Academy of Medicine

The New York Academy of Medicine through its Committee on Medical Education will hold its twenty-fifth Graduate Fortnight at its Headquarters in New York City, October 6–17, 1952. The general theme this year is "Hormones in Health and Disease," and the program includes Morning Panels, Hospital Clinics, Evening Sessions and a Scientific Exhibit. Dr. Franklin M. Hanger, F.A.C.P., is Chairman of the Graduate Fortnight Committee. Fifteen New York hospitals are coöperating on the clinic program. Many Fellows of the American College of Physicians are scheduled for papers, panels, clinics and demonstrations.

Fellows of the New York Academy of Medicine will be furnished registration cards without application. A registration card will be sent to Non-Fellows upon receipt of check, payable to the New York Academy of Medicine, for $10.00 for the entire program; $5.00 for the second week. Medical Officers of the Armed Service, in uniform, will be admitted without charge. Interns and residents will be admitted without charge, provided they present letters from their Chiefs of Service.

30th Annual Fall Clinical Conference, Kansas City Southwest Clinical Society

The 30th Annual Fall Clinical Conference of the Kansas City Southwest Clinical Society will be held at Kansas City, Mo., October 6–9, 1952. There is a long list of eminent guest speakers, including many Fellows of the American College of Physicians. The program consists of sectional lectures, panel discussions, scientific and technical exhibits.

Dr. Arthur Grollman, F.A.C.P., Dallas, Tex., has presentations on "Hypertension: Pathogenesis and Treatment" and "The Use and Abuse of Modern Drug Therapy," and he participates in a Clinical-Pathological Conference and in a Symposium on Gastric Ulcer.

Dr. John T. King, F.A.C.P., Baltimore, Md., has presentations on "Coronary Artery Disease" and "Digitalis Delirium," and he will participate in a Panel Discussion on "Chest Emergencies."

Dr. William A. Sodeman, F.A.C.P., New Orleans, La., has presentations on "Hepatitis" and "Some Pitfalls in the Management of the Cardiac Patient," and he is a participant in the Symposium on Gastric Ulcer.

Dr. Willard O. Thompson, F.A.C.P., Chicago, Ill., will have presentations on "Uses and Misuses of Sex Hormones" and "The Present Status of ACTH and Cortisone."

Conference Committee on Graduate Training in Internal Medicine

The Conference Committee on Graduate Training in Internal Medicine met at Chicago on June 9, 1952, with Dr. Walter Palmer, F.A.C.P., acting as Chairman. Those present in addition to Dr. Palmer were: Dr. Roy Scott, F.A.C.P., representing the American Board of Internal Medicine; Dr. LeRoy H. Sloan, F.A.C.P., Dr. Howard Wakefield, F.A.C.P., both of Chicago, and representing the American College of Physicians; Dr. Francis Wood, F.A.C.P., Philadelphia, Dr. Thomas M. Durant, F.A.C.P., Philadelphia, representing the Council on Medical Education and Hospitals of the American Medical Association; and Dr. Edward Leveroos, Associate Secretary of the Council on Medical Education and Hospitals.

The primary function of the Conference Committee on Graduate Training in Internal Medicine is to determine upon the approval of hospitals for residency training. Dr. Francis Wood is a new appointee succeeding Dr. William S. Middleton. Dr. Thomas Durant has now been appointed to succeed Dr. Scott as a representative of the American Board of Internal Medicine.

The following hospitals were approved for residency training in internal medicine:

Percy Jones Army Hospital, Battle Creek, Mich.
Valley Forge Army Hospital, Phoenixville, Pa.
Glockner-Penrose Hospital, Colorado Springs, Colo.
St. Vincent's Hospital, Bridgeport, Conn.
St. Francis Hospital, Miami Beach, Fla.
Mercer Hospital, Trenton, N. J.

The applications of several other hospitals were carefully examined and action deferred pending compliance with certain requirements, and further investigation. The Committee discussed the present requirements for approval, pointing out that these have not been revised for a number of years, resolved that if hospitals are to be approved at different levels, one, two or three years, the Committee should be able to advise the hospitals what the requirements are for each program. A special committee was appointed to bring in recommendations at the next meeting of Conference Committee.

The next meeting of the Committee will take place at the time and place of the next A. M. A. Annual Session, although it is possible that an interim meeting may need to be held. A new Chairman and new Secretary of the Conference Committee may be appointed on a yearly basis, at the time of the next meeting of said Conference Committee.

Isoniazid (Isonicotinic Acid Hydrazide) and Iproniazid (1-Isonicotinyl-2-Isopropylhydrazine) are being given to many patients with tuberculosis throughout the United States and in many other countries. Toxic reactions to both drugs have been reported and, undoubtedly, more will occur. However, it is unlikely that any single investigator will observe enough of these toxic reactions in the next few months to warrant publication. The committee on Therapy of the American Trudeau Society is anxious to collect reports of these toxic reactions, so that a consolidated report can be made available to the medical profession as soon as possible.

Any physician who is willing to submit such reports to the Committee is asked to send a brief case report to the Committee on Therapy, American Trudeau Society, c/o Dr. D. T. Carr, 102–110 Second Avenue Southwest, Rochester, Minnesota. The report should include the patient's name or initials, his age, sex, race, diagnosis, weight, the drug administered and its dosage, the duration of treatment, and a list of

other drugs being given at the same time. The toxic reaction should be described fully together with information as to its recurrence if the same drug was given later.

Copies of the consolidated report will be sent to all contributors, but will not be published in such a way as to preclude individual publications.

Argentine Medical Association Honors Dr. Robert C. Page

Dr. Robert Collier Page, F.A.C.P., Associate Clinical Professor, Industrial Medicine, New York University Post-Graduate Medical School, and General Medical Director, Standard Oil Company (N. J.), was presented with a gold medal during his recent tour of South America by the Argentine Medical Association, and was also made a foreign corresponding member of the Argentine Medical Association.

The award, said Dr. Juan Kaplan, President of the Association, was a tribute to Dr. Page as a medical man, as a scientist, organizer and writer for his work towards a better understanding regarding modern medicine between the nations of the Western Hemisphere.

Oklahoma Physicians Cited for Fifty Years of Service

In recent ceremonies in Oklahoma City, Dr. Lewis J. Moorman, F.A.C.P., and Dr. Everett S. Lain, F.A.C.P., were among twelve doctors who received gold lapel pins denoting fifty years in the practice of medicine. Dr. Lain had previously been the recipient of a gold medal and a diploma from the American Cancer Society in recognition of his work in the field of research. Dr. Moorman, former Dean of the University of Oklahoma Medical School, is the author of the well known books, *Tuberculosis and Genius* and *Pioneer Doctor*.

Recipients of Awards in the Scientific Exhibit of the A.M.A. Meeting

Numerous members of the College were cited by the Committee on Awards of the American Medical Association for their contributions to the Scientific Exhibit at the meeting of the Association held in Chicago in June. Dr. John R. Haserick (Associate), Cleveland, was one of those who jointly received the Hektoen Silver Medal for the exhibit on systemic lupus erythmatosus.

Among those who received Certificates of Merit in the various Sections were: Dr. Edward H. Robitzek, F.A.C.P., Staten Island, N. Y., (Diseases of the Chest) for the exhibit on treatment of tuberculosis with hydrazine derivatives of isonicotinic acid; Dr. Gordon M. Meade (Associate), Trudeau, N. Y., (Diseases of the Chest) for the exhibit on the antituberculosis activity of two hydrazines of isonicotinic acid; Dr. Carl Muschenheim, F.A.C.P., and Dr. Walsh McDermott, F.A.C.P., New York City, (Diseases of the Chest) for the exhibit on isonicotinic hydrazide ("nydrazid") in the treatment of tuberculosis; and Dr. David Adlersberg, F.A.C.P., New York City, (Gastro-Enterology and Proctology) for the exhibit on the role of Cortisone and ACTH in the treatment of therapy-resistant sprue.

Dr. Albert F. R. Andresen, F.A.C.P., Brooklyn, was the recipient of the Annual Alumni Medallion for Distinguished Service to Medicine at the Commencement Exercises on June 5 of the State University of New York College of Medicine in New York City (the former Long Island College of Medicine).

Dr. Andresen graduated from that institution, then known as the Long Island College of Medicine, in the class of 1907. He became early associated with that institution, and served it in many capacities. He began teaching there as Instructor

in Anatomy in 1909, Instructor in Gastro-enterology in 1910, and in 1919 he became Clinical Professor of Medicine and Director of the Department of Gastro-enterology in the hospital and clinic. In 1937 he served a year as Acting Professor of Medicine, later becoming Professor of Clinical Medicine, and in 1951, Clinical Professor Emeritus. The students to whom he taught the principles of Gastro-enterology number over 3,000 and are scattered over the entire country.

Dr. Andresen served many other hospitals and teaching institutions during his career, and was very active in local, state and national medical societies. He published more than 200 articles, chapters in several books, most of them dealing with the field of Gastro-enterology. He has been a Fellow of the American College of Physicians since 1921.

Dr. Edward L. Bortz, F.A.C.P., Philadelphia, Regent, was the official representative of the College at the Centennial Celebration of the American Pharmaceutical Association, held in the Bellevue-Stratford Hotel, Philadelphia, August 20.

Dr. S. O. Waife (Associate) has resigned as Director of Medical Education at the Philadelphia General Hospital to accept an appointment with the Lilly Research Laboratory, the Indianapolis General Hospital and the Indiana University School of Medicine.

Dr. Nelson G. Russell, Sr., F.A.C.P., Buffalo, N. Y., former College Governor for Western New York, received the Samuel P. Capen Alumni Award at the annual dinner of the University of Buffalo General Alumni Board held in June. The award was made to Dr. Russell, who is Emeritus Professor of Medicine and who joined the medical faculty in 1897, for his outstanding services to the University.

Dr. J. Roscoe Miller, F.A.C.P., Chicago, President of Northwestern University, was awarded the Alumni Medal by the Alumni Association of the University at its annual meeting June 11. The award is the highest honor of the Association and was bestowed on Dr. Miller for his "eminence in medical research and educational circles."

Brigadier General James Stevens Simmons, (MC), USA (Retired), F.A.C.P., Boston, Dean of the Harvard School of Public Health, was awarded the honorary degree of Doctor of Science at the 316th Commencement of Harvard College on June 19.

Dr. Daniel J. Glomset, F.A.C.P., Des Moines, was honored by the Iowa State Medical Society during its annual meeting for his research on cardiac conduction systems and for his work in establishing the State Medical Society's Speakers Bureau.

Dr. Emmet F. Horine, F.A.C.P., Brooks, Ky., received an honorary Master of Arts degree from the University of Cincinnati in May. The occasion was the 100th anniversary of the death of Dr. Daniel Drake, a pioneer physician and the founder of the Medical College of Ohio, which has become the Medical College of the University of Cincinnati. At the ceremonies, Dr. Horine, Historian of the Kentucky State Medical Association, spoke on "Cincinnatian Unique: Daniel Drake."

Dr. James H. Means, F.A.C.P., Boston, a former College President, received the 1952 Squibb Award in Endocrinology at the annual meeting of the Endocrine

Society in Chicago on June 6. The award was made in recognition of his work in the physiology, pathology, and metabolic functions of the thyroid gland.

Dr. Robert Wilson, Jr., F.A.C.P., Charleston, College Governor for South Carolina, has been elected Secretary of the South Carolina Medical Association.

Dr. Stanley P. Reimann, F.A.C.P., Philadelphia, was elected President of the American Association for Cancer Research at the society's recent annual meeting in Detroit.

At the recent annual meeting of the Massachusetts Heart Association, Dr. James C. McAdams, F.A.C.P., Fall River, was elected Vice President.

Dr. Harold Brandaleone, F.A.C.P., New York City, has been elected to the Vice Presidency of the Alumni Association of the New York University College of Medicine.

Dr. Carlisle Morse, F.A.C.P., Louisville, Ky., has been appointed a member of the Committee on Diabetes Detection and Education of the American Diabetes Association.

The Oregon State Medical Society has honored Dr. Charles E. Sears, F.A.C.P., Portland, by electing him an honorary member "in recognition of his long and distinguished service to the society and to the medical profession."

Dr. Virgil P. Sydenstricker, M.A.C.P., Augusta, Ga., has been elected to honorary membership in the Horse Shoe Club of London, the aims of which are to foster friendship between Americans and Englishmen interested in the cure and prevention of disease, to encourage exchange and clinical appointments between the two countries, and to provide hospitality for overseas visitors.

Dr. Benjamin M. Gasul, F.A.C.P., Chicago, was one of the speakers at the Second World Congress of Jewish Physicians, which convened in Israel, August 10–14. His topic was "Fundamental Problems in Congenital Heart Diseases."

Dr. Hyman I. Goldstein (Associate), Camden, N. J., has been awarded a diploma and elected an Honorary Member of La Sociedad Médica de Acapulco, Guerrero, Mexico. Dr. Goldstein addressed the Acapulco physicians on "Some Aspects of Diseases of the Gallbladder and Liver" and on "Angina Pectoris, Coronary Thrombosis and Myocardosis."

Dr. Milton J. Matzner, F.A.C.P., has been appointed Attending Gastroenterologist at the Brooklyn State Hospital, as of July 25, 1952.

Dr. J. Shirley Sweeney, F.A.C.P., Gainesville, Tex., was one of the guest speakers at a two-day postgraduate assembly sponsored by the University of Oklahoma in June. His lectures were on "Problems Pertaining to Diabetes Mellitus" and "The Value of Camps for Diabetic Children."

Dr. John J. Thorpe (Associate) has been appointed Assistant Medical Director of Esso Standard Oil Company, New York City. He had been a member of the Medical Staff of that organization since 1949. He is certified by the American Board of Internal Medicine, and presently is an Assistant Clinical Professor of Medicine at Cornell University Medical College.

Dr. James R. Shaw, F.A.C.P., has been appointed Chief, Division of Hospitals, Public Health Service of the Federal Security Agency. Dr. Shaw was formerly Medical Officer in Charge of the U. S. Public Health Service Hospital, Detroit, Mich. As Chief of the Division of Hospitals, he will have charge of the 22 hospitals, 19 outpatient clinics, and over 100 outpatient offices operated for the beneficiaries of the Public Health Service. This nation-wide chain of medical care facilities includes the narcotic hospitals at Lexington, Ky., and Fort Worth, Tex., and the hospital at Carville, La., for treating patients with Hansen's disease.

Dr. Thomas J. Rankin, F.A.C.P., Assistant Professor of Medicine, University of Kansas School of Medicine, transferred on August 1 from the Veterans Administration Hospital at Wichita, to the Veterans Administration Hospital at Kansas City, Mo., where he became Chief, Medical Service.

Dr. R. Carmichael Tilghman, F.A.C.P., Baltimore, College Governor for Maryland, was promoted on July 1 to Assistant Professor of Medicine at the Johns Hopkins University School of Medicine.

Dr. Nathaniel E. Reich, F.A.C.P., Brooklyn, has recently been promoted to Clinical Assistant Professor of Medicine at the State University of New York College of Medicine.

Dr. Jesse Frank Casey (Associate), heretofore Associate Professor of Psychiatry at the Menninger Foundation School of Psychiatry and Manager of the Veterans Administration Hospital at Topeka, has been transferred recently to the Headquarters of the Veterans Administration in Washington, D. C.

Dr. James Cotter Hirschberg (Associate), formerly of Denver, Colo., has recently been appointed Director, Department of Child Psychiatry, including the Southard School, of the Menninger Foundation, Topeka, Kans.

Among the new officers elected by the American Trudeau Society at its annual meeting in Boston are: Dr. David A. Cooper, F.A.C.P., Philadelphia, President, and Dr. Donald S. King, F.A.C.P., Brookline, Mass., President-Elect.

Dr. Sidney J. Shipman, F.A.C.P., San Francisco, was elected President of the National Tuberculosis Association when the Association held its annual meeting in Boston.

At the annual meeting of the Kansas Psychiatric Society, Dr. William Rottersman (Associate), of Topeka, was elected Vice President.

Dr. Frank N. Allan, F.A.C.P., Boston, and Dr. John A. Reed, F.A.C.P., Washington, were elected President and Secretary, respectively, of the American Diabetes Association at its annual convention held in Chicago in June.

At the annual meeting of the Medical Society of the State of New York, which was held in May in New York City, Dr. Alfred P. Ingegno, F.A.C.P., Brooklyn, was named Assistant Secretary. Among officers reëlected were: Dr. Walter P. Anderton, F.A.C.P., New York, Secretary; Dr. Maurice J. Dattelbaum, F.A.C.P., Brooklyn, Treasurer; Dr. Frederick W. Holcomb, Sr., F.A.C.P., Kingston, Speaker of the House of Delegates, and Dr. Frederick W. Williams, F.A.C.P., New York, Vice Speaker.

Dr. Walter C. Lobitz, Jr., F.A.C.P., Hanover, N. H., was elected Vice President of the Society for Investigative Dermatology at the annual meeting in Chicago, June 7–8.

Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., President of the American Medical Association, has been reëlected Chairman of the National Civilian Consultants Conference to the Air Force Surgeon General.

Dr. Thomas J. Coogan, F.A.C.P., Chicago, was elected President of the St. Louis University School of Medicine Alumni Association at its annual meeting in Chicago in June.

Dr. J. Asa Shield (Associate), Richmond, Va., has been named President-Elect of the Alumni Association of the Medical College of Virginia. Dr. Edward L. Alexander, Sr., F.A.C.P., Newport News, has been elected to the Board of Trustees.

Dr. Walter L. Palmer, F.A.C.P., Chicago, College Regent and former Governor for Illinois, was installed as President of the medical alumni of the University of Chicago when they met in Chicago in June.

The Medical Section of the Far East Command has conducted several conferences in Internal Medicine at the U. S. Army Hospital at Tokyo. These conferences are very similar to some of the Regional Meetings of the College but more particularly follow the type and organization of the postgraduate courses given by the College in the United States. These are two or three days in length. They appear also to show some of the continuing influence of the War-time Graduate Medical Meetings organized by the American College of Physicians and later joined by the American College of Surgeons and the American Medical Association, the purpose of which was to take graduate medical instruction to medical military officers in remote hospitals and installations. A copy of the program of one of the conferences at Tokyo reveals the names of many Fellows of the American College of Physicians who were participants.

Among the speakers at the Tuberculosis Symposium, sponsored by the Saranac Lake Medical Society and held at Saranac Lake, N. Y., July 14–18, were: Dr. Daniel M. Brumfiel, F.A.C.P., Dr. John N. Hayes, F.A.C.P., Dr. Edward N. Packard, F.A.C.P., and Dr. Arthur J. Vorwald, F.A.C.P., Saranac Lake; Dr. Frederick Beck,

F.A.C.P., and Dr. James Monroe, F.A.C.P., Ray Brook; Dr Gordon M. Meade (Associate) and Dr. Roger S. Mitchell, Jr., F.A.C.P., Trudeau.

Those participating in the International Congress of Physical Medicine, which met in London, England, July 14–18, included Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn.; Dr. Howard A. Rusk, F.A.C.P., New York City; Dr. Alvin B. C. Knudson, F.A.C.P., Washington, D. C.; and Dr. William D. Paul, F.A.C.P., Iowa City, Iowa.

Dr. Walter C. Alvarez, F.A.C.P., Chicago, Editor-in-Chief of *Modern Medicine*, and Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., Editor of the *Mississippi Valley Medical Journal*, are two of the participants in a Symposium on Medical Writing, which is part of the program of the Ninth Annual Meeting of American Medical Writers' Association, to be held in St. Louis, October 1.

Under the presidency of Dr. Daniel L. Sexton, F.A.C.P., St. Louis, the Mississippi Valley Medical Society will hold its Seventeenth Annual Meeting in St. Louis on October 1–3. Included on the program are: Dr. Wright R. Adams, F.A.C.P., and Dr. Walter C. Alvarez, F.A.C.P., Chicago; Dr. Henry A. Schroeder, Sr., F.A.C.P., Dr. Ralph A. Kinsella, A.C.P. Governor for Missouri, Dr. Carl V. Moore, F.A.C.P., Dr. Arthur E. Strauss, F.A.C.P., Dr. William A. Knight, Jr., (Associate), Dr. W. Barry Wood, Jr., F.A.C.P., and Dr. Goronwy O. Broun, F.A.C.P., all of St. Louis, and Dr. Philip S. Hench, F.A.C.P., Rochester, Minn.

Dr. Benjamin E. Goodrich, F.A.C.P., of the Henry Ford Hospital, Detroit, Mich., addressed the last annual meeting of the American Trudeau Society at Boston on "Pulmonary Period of Mitral Stenosis," and he was also a guest speaker at Clarksburg, W. Va., on April 17, at the invitation of the West Virginia State Medical Association and the West Virginia University School of Medicine.

OBITUARIES

DR. BYRON DARIUS BOWEN

Byron Darius Bowen, M.D., F.A.C.P., was born in Almond, N. Y., November 3, 1889, educated at Alfred University and in medicine at The University of Buffalo School of Medicine, receiving his M.D. in 1914. He pursued postgraduate work at Harvard Medical School and among London hospitals.

Dr. Bowen was Assistant Attending Physician at Erie County Hospital; he served at Buffalo General Hospital as Assistant in the Clinical Laboratory (1916–17), Clinical Assistant (1917–20), Metabolist (1920–22), Attending Physician and Metabolist (1933) and Chairman of the Outpatient Department (1938). He was also on the faculty of The University of Buffalo School of Medicine from 1918 forward, having been made Professor of Clinical Medicine in 1947. He retired in 1950.

He published many papers in various medical journals, most of his work being in the field of diabetes. He was President of The Buffalo Research Club (1946), a Councillor of The American Diabetes Association (1945–48), a member of The American Medical Association, New York State Medical Society, Buffalo Academy of Medicine, American Clinical and Climatological Association, American Society of Clinical Investigation, Society for Experimental Biology and Medicine, and of The Erie County Medical Society.

Dr. Bowen was a member of Sigma Xi and Alpha Omega Alpha fraternities, a Diplomate of The American Board of Internal Medicine and had been a Fellow of The American College of Physicians since 1922.

The citizens of Buffalo and the medical profession of Buffalo have sustained a distinct loss in the passing of Dr. Bowen, on December 30, 1951.

EDWARD C. REIFENSTEIN, M.D.,
Governor for Western New York

DR. EUGENE A. CASE

Dr. Eugene A. Case, F.A.C.P., died in the Delaware County Hospital, Drexel Hill, Pa., on April 20, 1952, at the age of 74. Dr. Case was born in New Albany, Ind., on November 17, 1877, but spent most of his medical life in the Philadelphia area.

He obtained his M.D. degree in 1908 from the Medico-Chirurgical College in Philadelphia and was Demonstrator and Associate Professor of Pathology at that institution from 1908 to 1916. After serving the college year of 1916–17 as Professor of Pathology and Bacteriology at the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C., he became, in 1919, Associate Professor of Pathology at the University of Pennsylvania Graduate School of Medicine, and was Professor of that subject until 1948.

Dr. Case was, in addition, Director of Laboratories of the Graduate School of the University of Pennsylvania from 1919 until 1949, as well as Pathologist of the Medico-Chirurgical Hospital in Philadelphia from 1908 to 1916. He also served as Pathologist at the Philadelphia General Hospital from 1909 to 1948, and was Consulting Pathologist at the American Hospital for Diseases of the Stomach, Philadelphia, and Mercer Hospital, Trenton, N. J. Upon his retirement from the University of Pennsylvania Graduate School of Medicine in 1948, Dr. Case became Consulting Pathologist at the Delaware County Hospital. During World War I, Dr. Case was a Lieutenant in the Medical Corps of the United States Navy, serving from 1917 to 1919.

In addition to holding memberships in the county and state medical societies, Doctor Case was a Fellow of the American Medical Association and of the College

of Physicians in Philadelphia. He was also a member of the Philadelphia Pathological Society, the American Society of Pathologists and Bacteriologists, and of Sigma Xi fraternity. He had been a Fellow of the American College of Physicians since 1930 and was a Diplomate of the American Board of Pathology.

DR. COURSEN BAXTER CONKLIN, SR.

Dr. Coursen Baxter Conklin, Sr., F.A.C.P., was born in Peekskill, New York, February 3, 1884. He died on March 2, 1952. He held the following degrees: B.S., 1916, M.A., 1928, George Washington University; M.D., 1907, George Washington University School of Medicine. Dr. Conklin's long professional career was spent almost entirely in the Washington area. He was a well known and respected pediatrician who also devoted considerable time to Internal Medicine. He lent his efforts generously for many years to the teaching staff at his alma mater, supervising the course in physical diagnosis for many years, and was listed as Clinical Professor of Medicine from 1909 to 1950. He was also a lecturer on the History of Medicine at George Washington University Medical School. During World War I, he was a lieutenant in the Medical Corps of the U. S. Army and in the Reserve attained the rank of lieutenant colonel.

Dr. Conklin became a Diplomate of the American Board of Internal Medicine in 1937 and a member of the American Academy of Pediatrics in 1938. He was a long-time member and Vice-President of the Washington Heart Association, Vice-President of the International Medical Club and of the Washington Medical and Surgical Society; a member of the House of Delegates of the American Medical Association; Chairman of the Committee on Legislation of the American Academy of Pediatrics, and was elected a Fellow of the American College of Physicians in 1923.

Perhaps the activity for which Dr. Conklin will be best remembered was his long and devoted service to the Medical Society of the District of Columbia. In the period prior to the employment of full time Executive Secretary for the Society, he served as Secretary for sixteen years and carried the onerous burden of the rapidly increasing responsibilities of this office willingly and enthusiastically. Few men would have given such devoted service. He was the founder of the *Medical Annals of the District of Columbia*, which he began in a small way in 1924 as a mimeographed bulletin recording the Society's activities. In 1931 this became the *Medical Annals*, and he was Managing Editor until 1938. He served on the Executive Board of this medical society from 1943 to 1949 and was a faithful attendant at its meetings. He was always eager to learn, as evidenced by his securing his academic degree nine years after his medical education had been completed, and his master's degree twelve years later, and was an interested and participating attendant at scientific professional meetings.

It is fair to say that during difficult times when the budget was small and difficult to work with, Dr. Conklin did much to keep the Medical Society of the District of Columbia functioning and keeping its proper place among the professional organizations of the District. It seemed sometimes he shouldered the burden almost alone, and the members of the Society and of the profession will remember with enduring gratitude his effective efforts for them. No stronger evidence could be given of his interest in medical learning than the fact that he attended a day-long Regional Meeting of the American College of Physicians in Baltimore the day preceding his death.

Many other things could be said about him. He lived in the spirit of the true physician, always willing to help the suffering regardless of financial reward. Indeed, in his early days, he was known to his friends as the "doctor to the poor." He was

always willing to lend a hand in a worthy enterprise and to carry his full load of responsibility. He never hesitated to speak his mind about what he thought was right. The profession has lost a loyal and devoted member who, in his quiet, unassuming way, rendered very unusual service.

JOHN MINOR, M.D., F.A.C.P.,
Governor for District of Columbia

DR. ISAAC GERBER

Dr. Isaac Gerber, F.A.C.P., an outstanding roentgenologist of Providence, R. I., and a Fellow of the American College of Physicians since 1931, died on February 17, 1952. Dr. Gerber had specialized in the practice of radiology during his entire professional career, which began when he opened his office in Providence in 1914. He was the first in this locality to confine his practice solely to radiology.

He was a graduate of the Harvard Medical School (1910) and received his postgraduate training at the Boston City Hospital and abroad. From 1916 to 1920 he was director of the X-ray Department of the Rhode Island Hospital and later became a consultant. He was also Consulting Roentgenologist to several other hospitals, both in the city of Providence and elsewhere in Rhode Island.

Dr. Gerber was a Diplomate of the American Board of Radiology, a Fellow of the American College of Radiology, a Past President of the New England Roentgen Ray Society, Vice-President of the Rhode Island Medical Society (1947–1948), and held memberships in the Providence Medical Association, the American Medical Association, the American Roentgen Ray Society, the American Radium Society, the Radiological Society of North America and the British Institute of Radiology.

He received an unusual honor during his life when his colleagues of the Miriam Hospital Staff of Providence established in 1948 a permanent annual Oration bearing his name.

For the last twenty-five years of his life he was afflicted with a progressive spinal cord ailment, yet he continued in the active practice of radiology until 1944 and in a constant attendance at medical meetings and conferences until his final illness. After retirement from his own practice, he resumed an active role in the X-ray Department of the Rhode Island Hospital by assisting there until 1948.

He did not confine his intellectual interests to radiology and its allied fields alone, but during his entire career manifested a knowledge of all branches of medicine, which came from a continuous study of the medical literature and a careful consideration and notation of the clinical aspects of patients referred to him for x-ray diagnosis or treatment. Apart from medical groups, he was an active participant in several community organizations.

The courage and indomitable will he exhibited in carrying on the above-listed activities when he was leading largely a wheel-chair existence, was a continual source of marvel and inspiration to his colleagues. Many sought his advice and were rewarded with rare judgment and friendly teaching.

In his passing there was lost not only a highly skilled specialist in roentgenology but also a beloved and respected friend of physician and patient alike.

IRVING A. BECK, M.D. (Associate)

DR. JULIUS GOTTLIEB

Dr. Julius Gottlieb, F.A.C.P., Lewiston, Maine, died February 17, 1952, at the age of 56, of coronary heart disease. Dr. Gottlieb was born in Jerusalem on January 2, 1896. He obtained his B.S. Degree from Harvard College in 1918, and his M.D. Degree from Boston University School of Medicine in 1924. He did postgraduate

study in Pathology and Bacteriology at Boston University in 1926 and 1927. He was a Diplomate of the National Board of Medical Examiners and of the American Board of Pathology, and had been a member of the American College of Physicians since 1932. The Boston University School of Medicine conferred an honorary doctor of science degree on him in 1924. He served on the faculty of that institution for several years, later becoming Assistant Professor of Postgraduate Pathology and Bacteriology at Tufts College Medical School, and still later Professor of Bacteriology at Colby College. He had been affiliated with the Augusta (Maine) General Hospital, Bath (Maine) Memorial Hospital, Brunswick (Maine) Hospital, Camden (Maine) Community Hospital, Franklin County Memorial Hospital in Farmington, Henrietta D. Goodall Hospital in Sanford, Gardiner (Maine) General Hospital, Knox County General Hospital in Rockland, Miles Memorial Hospital in Damariscotta, Redington Memorial Hospital, Skowhegan, Rumford (Maine) Community Hospital, St. Andrews Hospital in Boothbay Harbor, Sisters' Hospital and Thayer Hospital in Waterville, and the Central Maine General Hospital. He was a surgeon in the U. S. Public Health Service Reserve.

Dr. Gottlieb had been associate editor of the Maine Medical Journal. He was a member of the American College of Pathologists, and in 1933 was elected Chairman of the Maine State Cancer Committee. He retired from active practice and teaching during September, 1948.

DR. ROCKWELL M. KEMPTON

Dr. Rockwell M. Kempton, F.A.C.P., of Saginaw, Mich., died on April 5, 1952. Dr. Kempton's entire professional life was spent in the city of Saginaw where he went after graduating from the University of Michigan in 1919 and serving his internship and residency in the University Hospital at Ann Arbor. He also served as a resident physician on the Boston Floating Hospital.

In 1920 he became associated with the late Dr. James D. Bruce in Saginaw, at first doing general practice and later devoting his entire time to pediatrics. Here he pioneered many innovations in the St. Mary's and Saginaw General Hospitals.

Throughout the Saginaw Valley the doctor was widely respected and considered to be one of the foremost pediatricians in this area. Dr. Kempton's professional and teaching affiliations were many. He was at one time instructor in pediatrics at the University Hospital in Ann Arbor. He was later on the attending staff of St. Mary's Hospital in Saginaw and the Saginaw General Hospital. He was also on the attending staff and the Medical Board of St. Luke's Hospital in Saginaw and a Consultant from 1945 of the Saginaw County Hospital. From 1937 to 1941 he served as extramural lecturer in postgraduate medicine at the University of Michigan Medical School.

Dr. Kempton was a member of the Sigma Xi fraternity, Detroit Pediatric Society, Saginaw County Medical Society, the American Medical Association and a past president of the Pediatric Society of the University of Michigan. He was a Fellow of the American Academy of Pediatrics, a Diplomate of the American Board of Pediatrics and a Fellow of the American College of Physicians since 1926.

DOUGLAS DONALD, M.D., F.A.C.P.,
Governor for Michigan

DR. HUBERT CLEMENT KNAPP

Dr. Hubert Clement Knapp, F.A.C.P., died in Baltimore, December 31, 1951. A native of Fayetteville, N.Y., Dr. Knapp attended the College of Physicians and Surgeons of Baltimore, graduating in 1896. From 1900 he was Associate Professor of Medicine at the College of Physicians and Surgeons and, when that institution

merged with the University of Maryland School of Medicine in 1915, he became Associate Professor of Medicine of the University of Maryland, which rank he held until 1926. At one time he was Director of the Pasteur Department of the University of Maryland.

Dr. Knapp was a Visiting Physician at the Mercy Hospital and the Church Home and Hospital. He was physician to the Baltimore City Police Department and physician to the United Railway for fifteen years. In World War I Dr. Knapp was a captain and was Commanding Officer of the Field Laboratory of the 42nd Division from September 1917 to July 1918. In 1921 Dr. Knapp was made a Fellow of the College.

In 1942 Dr. Knapp retired because of arthritis. He died in his eightieth year.

R. CARMICHAEL TILGHMAN, M.D., F.A.C.P.,
Governor for Maryland

DR. LOUIS JOSEPH KROLL

Dr. Louis Joseph Kroll (Associate) died on February 28, 1952, at the age of thirty-nine. Dr. Kroll was born and educated in Baltimore, attending the Johns Hopkins University where he received his A.B. degree in 1932; and in 1936 he graduated from the University of Maryland School of Medicine. His hospital training was at the South Baltimore General Hospital, where he served as interne and medical resident between 1936 and 1939, thereafter, becoming an Associate Attending Physician at that institution. Dr. Kroll was also on the staff of the University Hospital and taught Physical Diagnosis at the University of Maryland School of Medicine. From 1940 to 1945 he was associated with the Beck Diagnostic Clinic. He became an Associate of the College in 1948.

For many years Dr. Kroll had suffered from chronic nephritis, and his professional work, of necessity, was modified because of his physical condition. He died of uremia in Baltimore.

R. CARMICHAEL TILGHMAN, M.D., F.A.C.P.,
Governor for Maryland

DR. GEORGE MINER MACKENZIE

George Miner Mackenzie, F.A.C.P., died suddenly on March 25, 1952, of a spontaneous rupture of the abdominal aorta while vacationing at Charlottesville, Virginia.

Dr. Mackenzie was born August 13, 1885, at Lawrenceville, N. J., took his A.B. at Columbia College in 1908 and his M.D. at Columbia University College of Physicians and Surgeons in 1913. After interning at the Presbyterian Hospital in New York (1913–1915), for two years he trained in Pathology and then became affiliated with the Department of Medicine at Columbia University, where as the first Associate Professor of Medicine on a full-time basis he was one of the first in this country to select academic medicine as a career.

In 1927 he resigned his post at Columbia to become Physician-in-chief and Director of Laboratories at the Mary Imogene Bassett Hospital at Cooperstown, N. Y. During the twenty years as head of this clinic he demonstrated the practicability of maintaining a teaching institution with academic activities in an isolated rural community; and the pattern of his organization centering around a group of salaried doctors with diverse interests has served subsequently as a model for others formulating a high quality of medical service to parts of the country far distant from metropolitan areas.

After his voluntary retirement from Cooperstown in 1947 he was affiliated with the Division of Laboratories and Research of the New York State Department of

Health, and was also Special Consultant to the Division of Public Health Grants under the National Institutes of Health.

Dr. Mackenzie was a pioneer in the field of Allergy, and made many notable basic contributions to the present concepts of serum disease and specific sensitization to bacterial antigens. He was also interested in the mechanism of hemolysis and was one of the first to formulate a modern classification of the hemoglobinurias. He was a highly trained bacteriologist as well as immunologist and published a number of studies on the carrier state and the bacterial variants that develop during the course of certain epidemics.

For many years he had been collecting material for a biography of Karl Landsteiner, for whom he had the highest esteem and affection. His untimely death has left this important work unfinished.

He was a member of many professional societies, among which are: American Medical Association (Fellow), Medical Society of the State of New York (President, Sixth District Branch, 1940–41), Otsego County Medical Society, New York State Association of Public Health Laboratories, Association of American Physicians, American Association of Pathologists and Bacteriologists, American Association of Immunologists, American Society for Clinical Investigation, American Society for the Study of Allergy, Society for the Study of Asthma and Allied Conditions, American Clinical and Climatological Association (Councilor), Society for Experimental Biology and Medicine, Interurban Clinical Club, Harvey Society, American Association for the Advancement of Science, and Society of American Bacteriologists. He became a Fellow of the American College of Physicians in 1942.

Dr. Mackenzie, in addition to his scientific and literary attainments, was an outstanding clinician, an inspiring teacher and a thoughtful student with keen discernment and healthy skepticism. His colleagues will long honor him for his high idealism, his selfless devotion to duty and his courage in maintaining principles in which he believed.

FRANKLIN M. HANGER, M.D., F.A.C.P.

DR. JOHN STANLEY NICKUM

Dr. John Stanley Nickum, F.A.C.P., age 60, died April 8, 1952, with an acute coronary occlusion at Bridgeport Hospital after collapsing in his office. He was a resident of Bridgeport, Connecticut, for 35 years and was a member of the Bridgeport Hospital staff for 30 years, where he rose to be chief of the medical service and consulting physician in medicine.

Dr. Nickum was born in Hellertown, Pennsylvania, on February 3, 1892; M.D., Tufts Medical College (1918); Bridgeport Hospital: Intern (1918–1919), Assistant Attending in Medicine (1921–1940), Attending Physician (1940–1947), Chief of Medical Service (1947–1949); Assistant Physician, Medical Service, City Dispensary (1919–1924); Consultant on Medical Service, Milford Hospital (1940–1949); retired (1949) from hospital service because of coronary occlusion. Dr. Nickum was Examiner, Medical Advisory Board No. 22, Connecticut Selective Service (1940–1944). In addition to memberships in state and local societies, Dr. Nickum was a Fellow of the American Medical Association, a member of the American Heart Association, and became a Fellow of the American College of Physicians in 1941.

Dr. Nickum is survived by his wife, Mrs. Elizabeth P. Rose Nickum, and three daughters. He was respected highly by his fellow physicians and patients alike. His was the fortunate ability to have a keen clinical acumen that required a minimum of laboratory support to arrive at a proper diagnosis that led to a practical course of treatment. He was a physician who considered the patient's welfare first and foremost. His passing will be felt deeply by his community.

JOHN C. LEONARD, M.D., F.A.C.P.,
Governor for Connecticut

Corticotropin
(ACTH)

Upjohn

Upjohn

THE AMERICAN COLLEGE OF PHYSICIANS

SCHEDULE OF POSTGRADUATE COURSES, AUTUMN, 1952

The following courses have been arranged through the generous cooperation of the directors and the institutions at which the courses will be given. Tuition fees for all courses will be: Members, $30.00; Non-members, $60.00. Full details of these courses may be obtained through the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa.

No. Course	Sept.	October				November				December				
	30–Oct. 4	6–11	13–18	20–24	27–31	3–7	10–15	17–21	24–29	1–6	8–12	15–20	22–27	
1. **RECENT TRENDS IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE:** Mount Sinai Hospital, New York, N. Y.; Arthur M. Master, M.D., F.A.C.P., and Charles K. Friedberg, M.D., F.A.C.P., Co-Directors	X								THANKSGIVING WEEK				CHRISTMAS WEEK	
2. **INTERNAL MEDICINE, SELECTED SUBJECTS:** University of Pittsburgh School of Medicine, Pittsburgh, Pa., Roy R. Snowden, M.D., F.A.C.P., Director		X												
3. **CARDIOVASCULAR DISEASE:** Emory University School of Medicine, Emory University, Ga.; R. Bruce Logue, M.D., F.A.C.P., Director				X										
4. **SELECTED TOPICS IN HEMATOLOGY:** New England Center Hospital, Boston, Mass.; William Dameshek, M.D., F.A.C.P., Director							X							
5. **INTERNAL MEDICINE, CORRELATION OF NEW AND EXISTING BASIC AND CLINICAL FACTORS IN DIAGNOSIS AND TREATMENT:** Presbyterian Hospital and the University of Illinois College of Medicine, Chicago, Ill.; Frank B. Kelly, M.D., F.A.C.P., Director								X						
6. **GASTRO-ENTEROLOGY:** University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Henry L. Bockus, M.D., F.A.C.P., Director										X				
7. **INTERNAL MEDICINE:** University of California School of Medicine, Medical Extension, at the Franklin Hospital, San Francisco, Calif.; Stacy R. Mettier, M.D., F.A.C.P., Director; H. Clare Shepardson, M.D., F.A.C.P., Co-Director											X			
8. **RECENT ADVANCES IN INTERNAL MEDICINE:** Johns Hopkins University and University of Maryland, Baltimore, Md.; Maurice C. Pincoffs, M.D., M.A.C.P., and A. McGehee Harvey, M.D., F.A.C.P., Co-Directors											8–13			

INDEX TO ADVERTISERS

September, 1952

NEW *Pfizer Sterajject Syringe*

holds 2 cartridge sizes

Sterajject

Sterajject Penicillin G Procaine Crystalline In Aqueous Suspension (300,000 units)

Sterajject Penicillin G Procaine Crystalline In Oil with 2% Aluminum Monostearate (300,000 units)

Sterajject Penicillin G Procaine Crystalline In Aqueous Suspension (1,000,000 units)

Sterajject Combiotic* Aqueous Suspension (600,000 units Penicillin G Procaine Crystalline, 0.5 Gm. Dihydrostreptomycin)

Sterajject Dihydrostreptomycin Sulfate Solution (1 gram)

Sterajject Streptomycin Sulfate Solution (1 gram)

2 cartridge sizes for only 1 syringe!

two cartridge sizes permit *full standard* antibiotic dosage

cartridges individually labeled

ready for immediate use

no reconstitution

for full details, ask your Pfizer Professional Service Representative

Sterajject Cartridges: *each one supplied with sterile needle, foil-wrapped*

introduced by Pfizer *world's largest producer of antibiotics*

*TRADEMARK, CHAS. PFIZER & CO., INC.

ANTIBIOTIC DIVISION • CHAS. PFIZER & CO., INC. • BROOKLYN 6, N. Y.

ANNALS OF INTERNAL MEDICINE

OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PHYSICIANS

Editorial Office—University Hospital, Baltimore 1, Maryland

Executive Office—4200 Pine Street, Philadelphia 4, Pa.

Place of Publication—Prince & Lemon Sts., Lancaster, Pa.

MANUSCRIPTS. All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the Editor. Bibliographic references are to conform to the following style:

4. Doe, J. E.: What I know about it, J. A. M. A. 96: 2005, 1931.

Six illustrations per article are allowed without cost to the author. Beyond this number the author must pay the actual cost of illustrations.

REPRINTS. For each article published, there will be furnished gratis fifty reprints without covers. An order slip for additional reprints, with a table showing cost, will be sent with galley proof to each contributor. If additional reprints over the first fifty are wanted the order slip must be returned to the printer at the time corrected galley proofs are sent to the Editor.

REVIEWS. Selected monographs and books in the field of internal medicine will be reviewed monthly in the ANNALS. Authors and publishers wishing to submit such material should send it to the Editor. Since it is not possible to review all books submitted, a monthly list of all those received will be published in the review section.

SUBSCRIPTION. This periodical is issued monthly, new volumes beginning with the January and July numbers of each year. Subscription price per annum, net postpaid: $10.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico, Philippine Islands, Central and South American Countries, and Spain; $7.00, in the above countries, to bona fide medical students, interns and residents; $11.00, other countries. Prices for back numbers furnished upon application. Single numbers, current volume, when available, $1.25. Checks should be drawn to the order of W. D. STROUD, M.D., Treasurer, and remitted through the Executive Secretary's Office.

BUSINESS CORRESPONDENCE. All correspondence relating to business matters, advertising, subscriptions to the ANNALS, inquiries concerning membership in the American College of Physicians, et cetera, should be addressed to the Executive Secretary. Books and reprints presented to the College Library should be addressed to the Executive Secretary.

LANCASTER PRESS, INC., LANCASTER, PA.